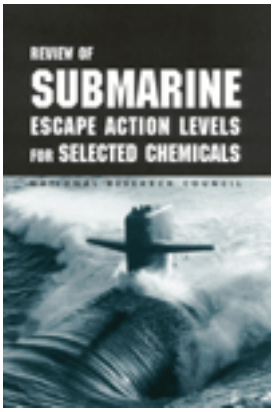

Review of Submarine Escape Action Levels for Selected Chemicals

Subcommittee on Submarine Escape Action Levels, Committee on Toxicology, Board on Environmental Studies and Toxicology, National Research Council

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REVIEW OF SUBMARINE ESCAPE ACTION LEVELS FOR SELECTED CHEMICALS

Subcommittee on Submarine Escape Action Levels
Committee on Toxicology
Board on Environmental Studies and Toxicology
Division on Earth and Life Studies
National Research Council

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Preface

The United States Navy seeks to protect crew members in disabled submarines from toxic effects caused by exposure to high concentrations of 8 gases: ammonia, carbon monoxide, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, sulfur dioxide, and chlorine. The toxic effects resulting from exposure to the gases could impede crew members' ability to escape after a serious accident. On-board fires would be anticipated as the principal sources of the first 7 gases; chlorine gas could be generated by the contact of seawater with a submarine's batteries.

The Navy Health Research Center's Toxicology Detachment has proposed submarine escape action levels (SEALs)—concentrations above which crew members' health and ability to escape could be jeopardized—for each gas. The Navy requested that the National Research Council (NRC) review independently the available toxicologic and epidemiologic data on the gases in question and evaluate the scientific validity of the Navy's proposed SEALs. The NRC assigned the project to its Committee on Toxicology, and assembled the Subcommittee on Submarine Escape Action Levels to prepare this report.

The subcommittee thanks Captain Kenneth Still (U.S. Navy), Commander Wayne Horn (U.S. Navy), and Lieutenant Cody Wilson (U.S. Naval Reserve) for their support of this project and for providing valuable background information. We also wish to express our gratitude to Dr. Paul Weathersby (U.S. Navy, Retired) and to Dr. Stephen Borron (International Toxicology Consultants) for providing information.

The subcommittee visited the nuclear attack submarine, *USS Dallas,* docked at the Navy's submarine base in Groton, Connecticut. Several members of the *USS Dallas's* crew were helpful in giving a crew's perspective on conditions aboard a submarine. The subcommittee members found the tour to be valuable to its work.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report: Stephen Borron, International Toxicology Consultants, Washington, District of Columbia; Aaron Cohen, Health Effects Institute, Cambridge, Massachusetts; David Dorman, CIIT Centers for Health Research, Research Triangle Park, North Carolina; Robert Phalen, University of California, Irvine, California; and Nga Tran, Johns Hopkins School of Public Health, Baltimore, Maryland.

Although the reviewers provided many constructive comments and suggestions, they were not asked to endorse the report's conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Joseph Borzelleca, Medical College of Virginia, Richmond, Virginia, who was appointed by NRC to ensure that an independent examination of this report was conducted in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

We are also grateful for the assistance of members of the NRC staff in the preparation of this report. The subcommittee acknowledges Abigail Stack, project director, and Kulbir Bakshi, program director of the Committee on Toxicology. Other staff members contributing to this report were James Reisa, director of the Board on Environmental Studies and Toxicology, Roberta Wedge, senior program officer; Eileen Abt, program officer; Susan Martel, program officer; Ruth Crossgrove, managing editor; Emily Smail, senior program assistant; and Jessica Brock, project assistant; and Kelly Clark, senior editorial assistant.

Finally, we thank all members of the subcommittee for their expertise and dedicated effort throughout the study.

Charles Hobbs, D.V.M
Chair, Subcommittee on Submarine Escape Action Levels
Bailus Walker Jr., Ph.D., M.P.H.
Chair, Committee on Toxicology

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Review of Submarine Escape Action Levels for Selected Chemicals

Summary

An event, such as a collision or explosion, that causes a submarine to become disabled can cause on-board fires, potentially exposing crew members to toxic concentrations of combustion products. The product gases include ammonia, carbon monoxide, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide. Chlorine can also be produced as a result of contact between seawater and submarine batteries. Exposure to any of those gases at high concentrations can cause toxic effects, particularly to the respiratory and central nervous systems, and can result in death. Exposures can also impair crew members' ability to escape from the submarine.

To protect crew members on disabled submarines, scientists at the U.S. Navy Health Research Center's Toxicology Detachment have proposed two exposure levels, called submarine escape action level (SEAL) 1 and SEAL 2, for each gas. SEAL 1 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 10 days without experiencing irreversible health effects. SEAL 2 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 24 hours without experiencing irreversible health effects. Exposures at SEAL 1 and SEAL 2 might produce moderate, reversible effects, such as irritation of the skin, eyes, and respiratory tract, but they will not impair the functions of the respiratory system and central nervous system to the extent of impairing the ability of crew members in a disabled submarine to escape or be rescued or perform specific tasks, such as shutting off a valve and using a fire extinguisher.

The primary objective of establishing SEALs is to protect crew members from adverse health effects—particularly to the respiratory and central nervous systems—from exposures to the combustion gases and chlorine. The Navy will use SEALs as one of many parameters in its Submarine Escape and Rescue Expert System model. That model takes into account several additional parameters, such as geographical position and depth of the submarine, number and medical condition of the crew members, ability to communicate with search and rescue forces, and compartment temperature, and is used by the senior officer to assist in making a decision on whether to escape from the disabled submarine.

STATEMENT OF TASK

Seeking to protect the safety of submariners, the chief of the Bureau of Medicine and Surgery requested that the National Research Council (NRC review the available toxicologic and epidemiologic data on eight gases that are likely to be produced in a disabled submarine and to evaluate independently the scientific validity of the Navy's proposed SEALs for those gases. The NRC assigned this project to the Committee on Toxicology (COT) and assembled the Subcommittee on Submarine Escape Action Levels, which prepared this report. The specific task of the subcommittee was to review the toxicologic, epidemiologic, and related data on ammonia, carbon monoxide, chlorine, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide to determine the scientific validity of the Navy's proposed SEALs. The subcommittee was also asked to consider the implications of exposures at hyperbaric conditions and potential interactions between the eight gases, identify deficiencies in the database relevant to setting SEALs for the eight gases, and recommend further research.

THE SUBCOMMITTEE'S APPROACH TO ITS CHARGE

The subcommittee evaluated human data from experimental, occupational, and epidemiologic studies; data from accident reports; and experimental-animal data (single and repeated exposures). The evaluations focused primarily on high-concentration inhalation exposure studies. The subcommittee's recommended SEALs are based solely on scientific data relevant to health effects.

In general, the subcommittee's approach was to recommend SEALs based on human data to avoid the need for incorporating an interspecies uncertainty factor commonly used in the derivation of exposure guidance levels from animal data. In its derivation of SEALs, the subcommittee did not incorporate an

intraspecies uncertainty factor for hypersusceptible individuals, because only healthy men are selected as submariners. Asthma is a disqualifying condition for submarine duty. However, some submariners might be hypersusceptible to the effects of the irritant gases and require the use of emergency air breathing devices (EABs). When a large number of crew members use EABs, expired air increases the pressure inside the submarine; this can increase the chance of decompression sickness. Because only a small number of crew members would be expected to use EABs due to hypersusceptibility to the gases, the expired air should not significantly increase the air pressure inside the submarine.

The subcommittee believes that for the irritant gases (i.e., ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide), the concentration of the gases to which crew members are exposed is more important than the exposure duration for determining toxicity. Additionally, for several of the irritant gases, an acclimation phenomenon has been well established.

In a disabled submarine, atmospheric pressure will likely be higher and temperature will likely be colder than the conditions used in most of the available studies from which SEALs were developed. The subcommittee emphasizes that its recommended SEALs are for normal atmospheric conditions (an atmospheric pressure of 1 and a temperature of 25°C). However, if the pressure increases in the disabled submarine, the SEAL values should be reduced in inverse proportion to the pressure increase.

The Navy should be aware that the altered atmospheric conditions on a disabled submarine would affect the toxicity of the gases. For example, cold temperatures will cause crew members to shiver; this will increase the rate of respiration because of an increase in metabolic rate. Lower air temperature might also result in the crew's breathing unconditioned air, which is a risk factor for lower-airway disease and airway hyperactivity. However, data are lacking on the precise magnitude of effects; therefore, the Navy should conduct research to determine the nature and magnitude of the effects from altered submarine atmospheric conditions.

Other parameters that should be taken into consideration are the distribution of the gases throughout the submarine; whether particular gases can be metabolized, absorbed, or neutralized by the crew; and whether the crew can acclimate to the gases at the concentrations present. Because of the lack of data on the effects of such parameters on toxicity of the gases, the subcommittee did not consider them in recommending SEALs. The senior officer on a disabled submarine should be aware of this limitation of the SEALs.

The subcommittee did not find information on the effects of hyperbaric conditions on Dräeger-tube (tubes that measure concentrations of specific gases) measurements and recommends that research be conducted to determine the effect of increased pressure on Dräeger-tube measurements. The results of that

research might show that values obtained for the gases using Dräeger tubes in a disabled submarine need to be corrected to an atmospheric pressure of 1 and 25°C.

THE SUBCOMMITTEE'S RECOMMENDED SUBMARINE ESCAPE ACTION LEVELS

After reviewing the available data on ammonia, carbon monoxide, chlorine, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide, the subcommittee concludes that the Navy's proposed SEALs for all gases, with the exception of SEALs for chlorine, would be protective of the health of personnel in a disabled submarine. In addition, the subcommittee concludes that SEALs for all the gases except chlorine could be set at levels higher than the Navy's proposed levels and still be protective of the health of crew members in a disabled submarine; at the subcommittee's recommended higher levels, eye or respiratory-tract irritation or central-nervous-system effects would not be intolerable or impair the performance of specific tasks, including the ability to escape. A comparison of the subcommittee's recommended SEALs with the Navy's proposed SEALs is presented in Table S-1.

ADDITIONAL RESEARCH RECOMMENDATIONS

There are virtually no data on the effects of exposure to a mixture of the eight toxic gases likely to be generated in a disabled submarine from fires and other conditions. The subcommittee recommends that research be conducted on potential health effects caused by exposure to mixtures of those gases. In particular, research should be conducted on the effects of exposure to a mixture of the six irritant gases —ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide. In addition, research should be conducted on the effects caused by the interaction of hydrogen cyanide, carbon monoxide, and hydrogen sulfide—gases that produce hypoxia.

As described in Chapter 1, the Navy has developed an approach for the management of mixtures of toxic gases in disabled submarines. That approach uses a cumulative exposure index (CEI), which assumes that the effects of exposure to mixtures of the irritant gases are additive but not synergistic. The subcommittee concludes that the use of the CEI approach is appropriate in protecting the health of the crew. That conclusion is consistent with the conclusions regarding the effects of exposure to mixtures of chemicals in other NRC

reports. The subcommittee recommends that hydrogen sulfide be added to the CEI for irritant gases. The subcommittee also recommends that a separate CEI be established for carbon monoxide and hydrogen cyanide, because the effects of exposure to these gases could be additive as well. The use of the CEI approach results in effectively lowering the SEALs when the toxicity of mixtures of gases is being assessed.

TABLE S-1 Comparison of the Navy's Proposed SEALs with the Subcommittee's Recommended SEALs

	Navy's Proposed SEALs (ppm)[a]		Subcommittee's Recommended SEALs (ppm)[b]	
Gas	SEAL 1	SEAL 2	SEAL 1	SEAL 2
Ammonia	25	75	75	125
Carbon monoxide	75	85	125	150
Chlorine	2	5	1	2.5
Hydrogen chloride	2.5	25	20	35
Hydrogen cyanide	1	4.5	10	15
Hydrogen sulfide	10	20	15	30
Nitrogen dioxide	0.5	1	5	10
Sulfur dioxide	3	6	20	30

[a]ppm, parts per million

[b]The subcommittee's recommended SEALs are for an atmospheric pressure of 1 at 25°C Values obtained for the gases using Dräeger tubes or other measurement devices in a disabled submarine might need to be corrected to an atmospheric pressure of 1 and 25°C.

The subcommittee recommends that the effects of altered environmental conditions (e.g., pressure, temperature, and humidity) on the toxicity of the gases on a disabled submarine be studied. Because fires on a disabled submarine will generate a large amount of particulate matter, research should be conducted on the effects of particles on the toxicity of gases.

The subcommittee recommends that the Navy give high priority to the development of battery-operated instruments that are more accurate than Dräeger tubes for measuring concentrations of the gaseous contaminants.

In addition to the general research recommendations presented above, the subcommittee recommends further research specific for each gas. Those recommendations are presented in the individual chapters that address each of the gases.

1

Introduction

Submarines have been used by the United States and other countries as weapons platforms for a century. Worldwide, there have been 102 known cases in which submarines have become disabled and have sunk in noncombat situations, leading to a loss of approximately 2,600 lives (Commander Wayne Horn, personal commun., U.S. Navy 2000). The most recent case, which occurred in August 2000, was the disablement and sinking of the *Kursk,* a Russian nuclear submarine, off of the northwestern coast of Russia in the Barents Sea. The submarine was taking part in a naval exercise. One hundred and eighteen crew members perished after a possible on-board explosion occurred (*Washington Post,* August 30, 2000). The last accident involving a U.S. submarine occurred in May 1968. The USS *Scorpion* sank with 99 men on board (Somers 1972). The cause of the sinking is unknown.

The most probable cause of a submarine sinking is flooding caused by an event that breaches the outer hull. The force required would have to be substantial. Potential causes include surface collision, grounding, external explosion, and catastrophic failure of a hull valve. It is likely that such an event also would start a fire within the submarine. The immediate concern for the crew is the release of toxic gases that are produced as the combustion products of on-board fires (U.S. Navy 1998). Human exposure to these gases can lead to adverse health effects, particularly respiratory and central nervous system effects, and even

death. Other concerns include the depletion of oxygen, largely from the fire, the accumulation of carbon dioxide, and the drop in temperature (U.S. Navy 1998).

Most accidents that lead to the disablement and sinking of submarines occur at a depth of less than 300 ft. Down to 600 ft, the crew can escape from the submarine, and down to 2,000 feet, the crew can be rescued (Brown 1999). To escape, a crew member enters the escape trunk and is subjected to pressure equalization (Bond et al. 1960). He then inflates a vest, takes a deep breath, and passes through the open escape hatch. Once outside the hatch, he starts releasing air from his lungs to avoid an air embolism and is carried rapidly to the surface by buoyancy from the vest. In the future, the U.S. Navy will use British submarine escape immersion suits (SEIS) instead of Steinke hoods or inflatable vests. The SEIS suits provide more protection to the crew and contain a one-man raft that can be deployed at the surface. Two crew members can escape together, and the process can be repeated every 15 min. Therefore, it would take approximately 13 hours for a crew of 100 to escape. Numerous risks are associated with escape, including nitrogen narcosis, barotrauma (a type of high-pressure injury to the ear drum, lungs, or bowel), arterial gas embolism, decompression sickness, hypothermia, and drowning (Benton et al. 1999; Parker et al. 2000). The United States and the United Kingdom have conducted submarine escape exercises from depths of 100–600 ft. Several subjects experienced decompression sickness and barotrauma (P.K.Weathersby, Ret., U.S. Navy, personal commun.). A comparison between the health effects associated with escaping from a disabled submarine and those associated with exposure to the eight gases is presented in Table 1–1.

It is difficult to quantify the risks associated with escape from a disabled submarine, however, it is known that attempting such an escape would be extremely dangerous. Because of the substantial risks associated with escape, the Navy's policy is that, if conditions allow, the crew of a submerged disabled submarine should wait for rescue (U.S. Navy 1998), which can be accomplished by the use of a deep submergence rescue vehicle (DSRV) or a submarine rescue chamber (SRC). The DSRV is a mini submarine that can go to a depth of 2,000 ft. It is attached to the disabled submarine, and 24 crew members are taken at a time from the submarine to a surface ship or to another submarine. The Navy currently has one DSRV, which is kept in San Diego, California. Depending on where in the world a disabled submarine is located, it can take up to 10 d for the DSRV to be transported to a site for rescue. The SRC can be used to a depth of 850 ft. It is lowered to the disabled submarine from a surface ship and can transport 6 crew members at a time to the surface.

As stated above, an event that leads to the disablement and sinking of a submarine is likely to also cause on-board fires. The toxic gases produced as combustion products could include ammonia, carbon monoxide, hydrogen

chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide. Chlorine gas also could be produced from the contact of saltwater with the submarine's batteries. To protect crew members, scientists at the Navy Health Research Center's Toxicology Detachment (NHRC/TD) have proposed preliminary exposure guidance levels, called submarine escape action levels (SEALs), for each of those gases.

TABLE 1–1 Health Effects Associated with Escape From a Disabled Submarine versus Exposure to Toxic Gases

Health Effects Associated with Escape[a]	Health Effects Associated with Exposure to the Gases Below the Recommended SEAL 2 Values
. Arterial gas embolism . Barotrauma . Decompression sickness . Drowning . Hypothermia . Nitrogen narcosis	. Moderate eye irritation and lacrimation from exposure to ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide. . Moderate respiratory effects from exposure to ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide. - Nasal irritation/lesions - Throat irritation - Chest irritation - Dyspnea - Transient pulmonary changes . Moderate central nervous system effects from exposure to carbon monoxide an hydrogen cyanide. - Headache - Abnormal vision - Decreased manual dexterity - Difficulty in concentrating - Syncope - Nausea and vomiting

[a]Most of these health effects are likely to be fatal to a significant number of crew members during an escape from a disabled submarine, particularly if the escape is conducted from a depth greater than 300 feet.

Under current Navy policy, when a submarine fire occurs, the crew is instructed to put on emergency air breathing devices (EABs) to prevent smoke inhalation and toxic gas exposure. When a large number of crew members use EABs, expired air increases the pressure inside the submarine, which can increase the chance of decompression sickness. Minimizing the use of EABs to prevent

an increase in air pressure inside the submarine is one objective of establishing SEALs; the crew would use EABs only when SEAL 2 is reached or exceeded. The SEALs were also established to protect crew members from short-term adverse health effects—particularly to the respiratory and central nervous system—that could reduce their chances of survival during and after an escape or rescue attempt.

STATEMENT OF TASK

To protect crew members on disabled submarines from adverse health effects caused by exposure to eight toxic gases, the Chief of the Bureau of Medicine and Surgery, U.S. Navy, requested that the National Research Council (NRC) review the available toxicity data on eight gases—ammonia, carbon monoxide, chlorine, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide—and evaluate the scientific validity of the Navy's proposed SEALs. NRC assigned the project to the Committee on Toxicology, and assembled the Subcommittee on Submarine Escape Action Levels. The specific task to the subcommittee was to review the toxicologic, epidemiologic, and related data to assess the validity of the Navy's proposed SEALs. The subcommittee also was to consider the implications of exposures at hyperbaric conditions and the potential interactions for atmospheric components. Deficiencies in the database relevant to setting SEALs for the gases were to be identified and, where appropriate, recommendations for research were to be made.

DEFINITIONS OF SEALS

Two SEALs are proposed for each of the eight gases that maybe generated on a disabled submarine as a result of fires or contact of saltwater with the submarine's batteries. SEAL 1 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 10 d without experiencing irreversible health effects. SEAL 2 is defined as the maximum concentration of a gas in a disabled submarine below which healthy submariners can be exposed for up to 24 h without experiencing irreversible health effects. Exposures at SEAL 1 and SEAL 2 might produce moderate, reversible effects, such as irritation of the skin, eyes, and respiratory tract, but they will not impair the functions of the respiratory system and central nervous system to the extent that impair the ability of submariners in a disabled submarine to escape or be rescued or perform specific tasks, such as shutting off a valve and using a fire extinguisher.

SEALs do not represent hard lines between safe and unsafe concentrations. If a SEAL is exceeded, some people should expect to be adversely affected.

The SEALs are based solely on scientific data relevant to health effects. Some surviving crew members in a disabled submarine are expected to perform light-to-moderate physical work and that is considered in the derivation of SEALs. It is inappropriate to use SEALs for routine exposures in a normally operating submarine.

The Navy will use the subcommittee's SEALs as one of many parameters in its Submarine Escape and Rescue Expert System model. That model takes into account several additional parameters, such as geographical position and depth of the submarine, number and medical condition of the crew members, the ability to communicate with search and rescue forces, and compartment temperature, and is used by the senior officer to assist in making a decision on whether to escape from the disabled submarine.

The decision to escape from the submarine is a military-management decision that involves many considerations, which are beyond the charge and expertise of the subcommittee. SEALs are not standards or judgments of acceptable risk and must not be so construed. They are the subcommittee's best judgment based on available evidence of exposure concentrations at which submariners can continue to function in an emergency situation in an environment of a disabled submarine and be unlikely to suffer irreversible effects. Like all reports of the National Research Council, this report contains only advisory information and recommendations.

THE ON-BOARD POPULATION

The U.S. Navy submariner population currently consists of an all-male, generally healthy group (personal communication, Commander Wayne Horn, U.S. Navy 2000). The average age of enlisted men is 26, and the average for officers is 31. The men are screened before assignment to a submarine for physical fitness and chronic health problems (e.g., neurologic, cardiovascular, respiratory).

Since 1938, asthma has been a disqualifying condition for submarine duty. However, a recent study reported that there is a 0.16% annual-period prevalence in the active duty enlisted Atlantic Fleet Submarine Force (Sims et al. 1999). Because asthma can develop in people during their 20s and 30s, it is possible that the condition can be diagnosed in some individuals after they are assigned to submarine duty. In most cases, submarine crew members who do have asthma exhibit only mild symptoms. It is not known whether the submarine atmosphere poses an occupational asthma risk Crew members with asthma are likely to be

more susceptible to toxic gases found in disabled submarines than would those without the condition.

THE SUBMARINE ATMOSPHERE

Today's nuclear submarines can stay submerged for up to 90 d, although a typical patrol is approximately 60 d (Davies 1973). One reason for long periods of submergence is that the nuclear core requires no air to generate power. Another reason is that atmosphere control systems renew the air for respiration. The systems produce oxygen by electrolysis of seawater; remove carbon dioxide by chemical scrubbing; remove carbon monoxide and hydrogen by catalytic oxidation; and remove dusts, aerosols, and some toxic contaminants by active and passive filters and by electrostatic precipitation (Davies 1973). Because the concentration of oxygen in a submarine is 17–20%, the risk of fire is somewhat lower than at the surface. Air at sea level is 20.95% oxygen. Submarine air is 0.3– 0.5% carbon dioxide, compared with 0.033% in ambient air at sea level.

Submarines are equipped with mass spectrometers and nondispersive infra-red spectrophotometers that, under normal operating conditions, continuously monitor the atmosphere for compounds such as oxygen, hydrogen, carbon monoxide, carbon dioxide, water vapor, and three fluorocarbons (NRC 1988). Submarines are also equipped with colorimetric detection tubes (Dräeger tubes). Submarine atmospheres also contain trace concentrations of many volatile organic compounds, including long-chain aliphatic hydrocarbons, aromatic compounds, and halocarbons (Knight et al. 1989). It should be noted that submariners live for periods of up to several months in a totally enclosed and isolated environment beneath the sea. Any exposure to contaminants occurs 24 h/d for up to 90 d; the crew has no respite or periods of recovery away from these conditions as do workers in traditional occupational settings. Chronic exposure to these trace contaminants is not believed to be toxic to submarine crews (Davies 1973). Detailed listings of the major atmospheric contaminants found in nuclear submarines and their sources can be found in Davies (1973) and NRC (1988).

In the event of a submarine fire, crew members are likely to be exposed to higher than normal concentrations of ammonia, carbon monoxide, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide, and possibly to hydrogen cyanide gas. Exposure to chlorine gas can occur if saltwater is introduced into the battery compartment. In a disabled submarine, it is probable that the spectrophotometers used to monitor atmospheric contaminants no longer function because of power loss. Additionally, if power is lost, air would no longer circulate through the scrubbers; the air would become stagnant, leading to increased concentrations of contaminants. To monitor contaminants, the

crew is instructed to use Dräeger tubes, which can indicate a value up to 30% lower or higher than the actual gas concentration.

If a submarine becomes disabled, atmospheric pressure could rise due to increased flooding and any use of EABs. The increased pressure can lead to decompression sickness in crew members and reduce the likelihood of a successful rescue (Shake et al. 1995; Eckenhoff 1984). Development of decompression sickness symptoms, such as the bends and air embolisms, is a major risk associated with escape from a disabled submarine. The higher the internal pressure in the disabled submarine and the greater the escape depth, the greater is the risk of developing decompression sickness. Figure 1–1 illustrates the relationship between the internal pressure of a disabled submarine, its depth, and the percentage of crew members who are likely to suffer from decompression sickness.

THE NAVY'S INSTRUCTIONS FOR THE MANAGEMENT OF TOXIC GASES

The Navy's instructions for the management of toxic gases, including the use of SEAL 1 and SEAL 2, are shown in Box 1–1. The instructions use a cumulative exposure index (CEI) approach, which considers the combined exposure to the irritant gases—ammonia, chlorine, hydrogen chloride, sulfur dioxide, and nitrogen dioxide—to result in additive and not synergistic effects. Thus, when mixtures of these gases are present, the CEI results in effectively lowering the SEAL 1 and SEAL 2 for each gas. The subcommittee believes the Navy's approach of assuming that combined exposure to several gases resulting in additive and not synergistic effects is appropriate, and this approach is likely to protect the health of the crew. The approach is consistent with those recommended in other NRC reports (NRC 1992, 1994).

The Navy's instructions in Box 1–1 allow for individual crew members to wear EABs if symptoms are severe. Thus, susceptible crew members can be protected without as much danger of increasing the pressure in the submarine as would happen if the entire crew were to wear EABs. Crew members wearing EABs are instructed to remove them each hour, as concentrations of some gases are likely to decrease overtime because of adsorption of some gases to submarine surfaces or because of the solubility of some gases in water.

THE SUBCOMMITTEE'S APPROACH TO ITS CHARGE

The subcommittee evaluated human data from experimental, occupational, and epidemiologic studies; data from accident reports; and experimental-animal

data (single and repeated exposures). The evaluations focused primarily on high-concentration inhalation exposure studies that measured respiratory and central nervous system effects. In general, the subcommittee's approach was to recommend SEALs based directly on human data to avoid the need for incorporating uncertainty factors commonly used in the derivation of exposure guidance levels from animal data. Minor health effects (e.g., respiratory tract and eye irritation) are excluded from consideration as long as they do not become intolerable, cause irreversible effects, or impair a crew's ability to escape.

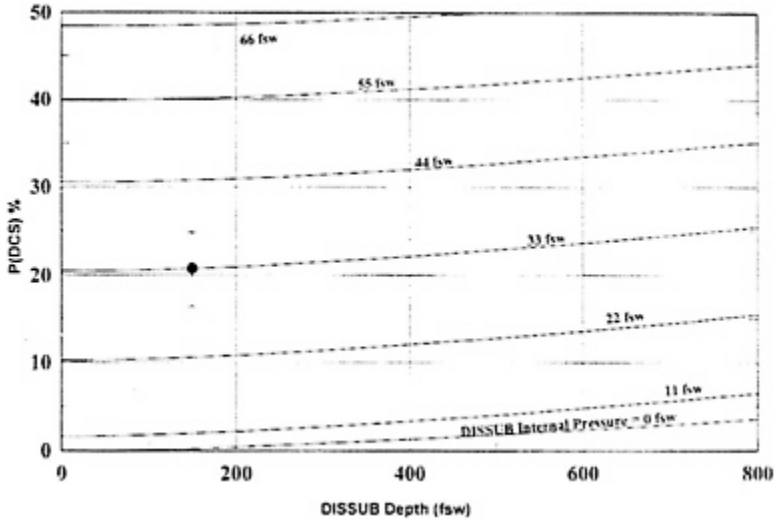

FIGURE 1–1 Relationship between the depth of the disabled submarine, the internal pressure of the submarine, and the percentage of the crew members likely to suffer from decompression sickness. Abbreviations: DCS, decompression sickness; DISSUB, disabled submarine; fsw, feet seawater. Source: Parker et al. 2000. Reprinted with permission from *Aviation Space and Environmental Medicine,* copyright 2000, Aerospace Medical Association, Alexandria, Virginia.

The subcommittee believes that its recommended SEALs might produce health effects such as moderate irritation of respiratory tract, eyes, skin, or other moderate reversible effects, but would not produce any irreversible health effects in the submariners. The subcommittee did not incorporate an uncertainty factor for hypersusceptible individuals, including asthmatics, because as discussed above, the submariner population is healthy and asthma is a disqualifying condition for submarine duty. However, it is possible that some crew members may be hypersusceptible to the effects of the irritant gases or become mildly asth

matic during the course of their employment as a submariner, and it might be necessary for those individuals to wear EABs at concentrations below the SEAL 2. Because only a small number of crew members would be expected to use EABs in that circumstance, the expired air should not significantly increase the air pressure inside the submarine.

Crew members on a disabled submarine would not be expected to be engaged in heavy physical activity (Captain K.Still, U.S. Navy, personal commun., 2001). Some crew members would need to do light work, such as the use of a fire extinguisher. However, the majority of crew members on a disabled submarine would be asked to lay down in their bunks and keep their eyes closed, which would serve to conserve oxygen, reduce carbon dioxide production, reduce the amount of toxic gases that the submariners would inhale, and reduce eye irritation.

The subcommittee believes that for the irritant gases (i.e., ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide), the exposure concentration of the gases is more important than the exposure duration for determining toxicity, particularly for durations up to 24 h. Additionally, for several of the irritant gases reviewed in this report, an acclimation phenomenon has been well established.

Particulate matter, with significant toxicity, could be generated from onboard fires. The subcommittee believes it is possible that high-particle concentrations may interact with some of the gases and increase their toxicity. However, the subcommittee did not find data on such interactions and, therefore, was not able to consider them in recommending the SEALs.

In a disabled submarine, temperatures will likely be colder and atmospheric pressures higher than the normal atmospheric conditions used for studies from which SEALs were developed. The subcommittee emphasizes that its recommendations for SEALs are for an atmospheric pressure of 1 and a temperature of 25°C. Corrections for altered temperature and pressure will need to be made. If the pressure increases in the disabled submarine, the SEAL values should be reduced in inverse proportion to the pressure increase. The subcommittee did not find information on the effects of hyperbaric conditions on Dräeger-tube measurements. Values obtained for the gases using Dräeger tubes in a disabled submarine might need to be corrected to an atmospheric pressure of 1 and 25°C.

The Navy should be aware that the altered atmospheric conditions on a disabled submarine would affect the toxicity of the gases. For example, cold temperatures will cause crew members to shiver, which will increase the minute volume of ventilation due to an increase in metabolic rate. Lower air temperature may also result in the crew breathing unconditioned air, which is a risk factor for lower-airway disease and airway hyperactivity.

BOX 1–1 THE MANAGEMENT OF TOXIC GASES ON A DISABLED SUBMARINE

1. OVERVIEW

A. The aims of the toxic-gas management routine are as follows:

1. To protect survivors from the short-term effects of toxic gases in the disabled submarine atmosphere—particularly injury to the respiratory and central nervous systems, which wold significantly reduce the chances of survival during and following an escape or rescue attempt.
2. To minimize the requirement to wear EAB (emergency air breathing) masks.

2. SUBMARINE ESCAPE ACTIONS LEVELS (SEALs)

A. SEAL 1—Below this limit survivors can remain in the compartment without wearing respiratory protection for a maximum period of 10 d. Respiratory or nervous functions should not be impaired sufficiently to significantly increase the risks of escape or rescue. Above this level (but below SEAL 2) the atmosphere is still breathable for 24 hours without wearing EABs.

B. SEAL 2—At this level survivors are required to wear EABs because significant impairment to respiratory or nervous functions will occur if they breathe the atmosphere.

C. Five of the gases that can be measured act as respiratory irritants and their effects are considered to be additive. A Cumulative Effects Index (CEI) can be calculated for each SEAL, as shown below. If a CEI exceeds 1, the resulting action should be the same as if the SEAL for individual gas has been exceeded.

3. DISABLED SUBMARINE TOXIC GAS MANAGEMENT ROUTINE

A. If EABs are being worn, it is important to avoid unnecessarily pressurizing the boat. It is therefore important to decide early if it is safe to remove them. IF EABs ARE BEING WORN AND THE SOURCE OF TOXIC GAS IS CONTROLLED (FIRE EXTINGUISHED, SPILL CONTAINED), UNDERTAKE A TOXIC GAS SURVEY AT THE EARLIEST OPPORTUNITY.

B. If EABs are not being worn, this can be postponed to a more convenient time.

1. Survey the following gases with Dräeger tubes (*indicates respiratory irritant):

   Carbon Monoxide (CO)
   Hydrogen Cyanide (HCN)
   Hydrogen Chloride (HCl)*
   Sulfur Dioxide (SO_2)*
   Chlorine (Cl_2)*
   Oxides of Nitrogen (NO_x)*
   Ammonia (NH_3)*

2. Measure each gas in the following locations (or nearest space if it is inaccessible): Control Room, second level passageway outside Wardroom, Torpedo Room (aft end) and enter the results below.

Gas	Control Room (X)	Outside Wardroom (Y)	Torpedo Room (Z)
CO	ppm	ppm	ppm
HCN	ppm	ppm	ppm
NH_3	ppm	ppm	ppm
Cl_2	ppm	ppm	ppm
HCl	ppm	ppm	ppm
SO_2	ppm	ppm	ppm
NO_x	ppm	ppm	ppm

3. Average the three values for each gas (add them together and divide the total by three) and enter the result in column two of the table below. In column four, for each respiratory irritant, divide the average value (A_{NH3}, A_{CL2}, etc.) by its SEAL 1. Calculate the Cumulative Effects Index 1 (CEI 1) by adding the values together. Enter the total at the bottom of the column. Do the same for CEI 2 using SEAL 2 instead of SEAL 1 in column 6. A CEI is exceeded if the value is greater than 1.

Gas	Average= (X+Y+Z)/3	SEAL 1	CEI 1	SEAL 2	CEI 2
CO		75		85	
HCN		1		4.5	
NH_3	(A_{NH3})	25		75	
Cl_2	(A_{CL2})	2		5	
HCl	(A_{HCl})	2.5		25	
SO_2	(A_{SO2})	3		6	
NO_x	(A_{NOX})	0.5		1	
TOTAL					

C. If SEAL 2 for any gas or the CEI 2 has been exceeded, DON OR REMAIN ON EABs, prepare the trunk and start to escape unless there is either a small number of survivors (15–20) or contact has been made with rescue forces.

D. If neither SEAL 2 for any gas or CEI 2 has been exceeded, but SEAL 1 for any gas or the CEI 1 has been exceeded, REMOVE EABs. If there are fewer than 20 survivors, wait 24 hours and don EABs. Remain on EABs until rescue or escape. If there are 20 or more survivors, assume that 8 men will escape per hour and plan to start escaping so that the last man is out in 24 hours. One hour before starting to escape, repeat the toxic gas survey and only commence escapes if a SEAL 1 or CEI 1 is still exceeded.[1]

E. Because Dräeger tubes are not precise and not all gases can be measured, survivors may experience respiratory or nervous symptoms if SEAL 1 has not been exceeded. If the symptoms are severe, such as uncomfortable coughing, wheezing, shortness of breath, severe headache, or streaming eyes, place those so affected on EABs. Each hour, those on EABs should try breathing the submarine atmosphere and only return to EABs if severe symptoms return. AT ANY TIME, IF MORE THAN 30% OF SURVIVORS ARE ON EABs, PROCEED AS IF SEAL 2 HAS BEEN EXCEEDED.

F. If SEAL 1 has not been exceeded, and fewer than 30% of the survivors are on EABs, repeat the toxic gas survey each 24 hours for as long as sufficient Dräeger tubes remain.

[1]When SEAL values are exceeded, the senior officer on a disabled submarine might decide to begin an escape. However, this decision is based on many parameters in addition to the SEAL values (personal commun., K.Still, U.S. Navy 2001). Source: U.S. Navy. Naval Sea System Command Technical Publication 59594-AP-SAR-010. SSN688 Class Guard Book, Disabled Submarine Survival Guide, Forward Escape Trunk Interim: October 30, 2000.

The subcommittee recognizes that the senior officer aboard a disabled submarine will have to consider many factors when deciding whether the crew should try to escape or await rescue. Such factors include the depth and condition of the submarine; the proximity of a rescue vehicle; the number and physical condition of survivors; the temperature of the sea water; the ambient pressure inside the submarine; the presence of airborne particles; and the concentrations of oxygen, carbon dioxide, and toxic gases. Factors specific to the toxic gases include which gases are present and how they are distributed throughout the submarine; whether the gases can be metabolized, absorbed, or neutralized by the crew; and whether the crew can acclimate to the gases at the concentrations present. Because of the lack of data on the effects of these parameters on toxicity of the gases, it is not possible to recommend SEALs for each gas for every potential scenario; therefore, the subcommittee did not consider factors such as those described above in recommending the SEALs. The senior officer on a disabled submarine should be aware of this limitation of the SEALs.

COMPARISONS BETWEEN SEALS AND EXISTING EXPOSURE GUIDANCE LEVELS

In chapters 2–9, the subcommittee presents existing exposure guidance levels for each gas, which have been recommended by various regulatory agencies and other organizations. Those levels include the NRC's emergency exposure guidance levels (EEGLs), continuous exposure guidance levels (CEGLs), spacecraft maximum allowable concentrations (SMACs), acute exposure guidance levels

(AEGLs), the American Industrial Health Association's emergency response planning guidelines (ERPGs), the American Conference of Governmental Industrial Hygienists' Threshold Limit Values (TLVs), and the National Institute for Occupational Safety and Health's immediately dangerous to life and health values (IDLHs). The AEGLs, ERPG, TLV, and IDLH values are developed for the general public or workers and take into account susceptible subpopulations, such as asthmatics and children. As described above, SEALs are developed specifically for submariners, who are healthy male adults with no history of asthma or other chronic medical conditions. Therefore, the subcommittee does not believe that it is appropriate to compare the SEALs to the AEGLs, ERPGs, TLVs, and IDLH values. Like the SEALs, the SMACs were developed for a healthy subpopulation, in this case astronauts. However, SMACs allow only mild irritation of the eyes, skin, and respiratory tract or mild central nervous system effects, whereas SEALs allow moderate reversible health effects. Additionally, SMACs take into account the changes in the astronauts' physiological systems that they will experience from working under microgravity conditions. Therefore, EEGLs are the most relevant guidance levels to compare to the SEALs. EEGLs were developed for emergency situations involving healthy military personnel. An important difference between the EEGLs and the SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for the EEGLs. Therefore, the SEALs are higher than the corresponding EEGLs.

ORGANIZATION OF THE REPORT

This report has nine chapters in addition to this introduction. Chapters 2 to 9 contain the subcommittee's reviews of the available toxicologic, epidemiologic, and other data on ammonia, carbon monoxide, chlorine, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide, respectively, its evaluations of the Navy's proposed SEALs for each of the gases, and research needs for each of the gases. Chapter 10 contains the subcommittee's conclusions and recommendations.

REFERENCES

Benton, P.J., T.J.R.Francis, and R.J.Pethybridge. 1999. Spirometric indices and the risk of pulmonary barotrauma in submarine escape training. Undersea and Hyperbaric Medicine. 26(4):213–217.

Bond, G.F., R.D.Workman, and W.F.Mazzone. 1960. Deep Submarine Escape. Report No. 346. Vol. XIX, No. 21. New London, CT: U.S. Naval Medical Research Laboratory.

Brown, D.C. 1999. Operational medicine. Submarine escape and rescue in today's Royal Navy. J.R.Nav. Med. Serv. 85(3):145–149.

Davies, D.M. 1973. Sixty days in a submarine: The pathophysiological and metabolic cost. J.R.Coll. Physicians. Lond. 7(2):132–144.

Eckenhoff, R.G. 1984. Pressurized Submarine Rescue. NSMRL Report 1021. NTIS/AD-A143 348/1. Groton, CT: Naval Submarine Medical Research Laboratory.

Knight, D.R., D.V.Tappan, J.S.Bowman, H.J.O'Neill, and S.M.Gordon. 1989. Submarine atmospheres. Toxicol. Lett. 49(2–3):243–251.

NRC (National Research Council). 1988. Submarine Air Quality. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Science and Judgment in Risk Assessment. Washington, DC: National Academy Press.

Parker, E.C., R.Ball, P.M.Tibbles, and P.K.Weathersby. 2000. Escape from a disabled submarine: Decompression sickness risk estimation. Aviat. Space Environ. Med. 71(2):109–114.

Shake, C.L., P.K.Weathersby, B.G.Caras, and J.Parker. 1995. Helium-Nitrogen-Oxygen: Isobaric Shift and Saturation Decompression. NSMRL Report 1196. NTIS/ AD-A292 639/2. Groton, CT: Naval Submarine Medical Research Laboratory.

Sims, J.R., P.M.Tibbles, and R.P.Jackman. 1999. A descriptive analysis of asthma in the U.S. Navy Submarine Force. Aviat. Space Environ. Med. 70(12):1214–1218.

Somers, C.L. 1972. Submarine disasters in peacetime, 1900–1971. U.S. Naval Institute Proceedings, Naval Review 1972:319–329.

U.S. Navy. 1998. Memorandum from N.A.Carlson, Acting Commanding Officer, Naval Submarine Medical Research Laboratory to Officer in Charge, Naval Medical Research Institute Toxicity Detachment. Subject: The Management of Toxic Gases in a Disabled Submarine. March 2, 1998.

US. Navy. 2000. SSN688 Class Guard Book, Disabled Submarine Survival Guide, Forward Escape Trunk, Naval Sea System Command Technical Pub. S9594-APSAR-010. October 30, 2000.

Washington Post. 2000. US. theory On-board blast sank sub; analysts discount possibility of negligent Russian crew or maintenance flaws. A12, August 30, 2000.

2

Ammonia

This chapter reviews physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on ammonia. The Subcommittee on Submarine Escape Action Levels used the information to assess health risk to Navy personnel aboard a disabled submarine and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and research relevant for determining the health risk attributable to exposure to ammonia.

BACKGROUND INFORMATION

The subcommittee reviewed data that came primarily from human experimental studies and from toxicity studies in various animal species. The evaluation focused on inhalation exposure studies that measured respiratory irritation and tolerance to odor. Human case studies, accident reports, and epidemiologic studies of industrial exposures were extensive but of limited use to the subcommittee because they lack quantitative exposure measurements. Controlled human experiments were most important to the subcommittee for establishing the SEALs for ammonia. There appears to be a broad range of sensitivity to ammonia's pungent odor and in irritation caused by exposures to low concentrations

of ammonia. The odor threshold for ammonia is reported at 5–50 ppm (parts per million); the perception threshold for irritation is reported at 30–50 ppm (Wands 1981; WHO 1986). Intense irritation to the eyes, nose, and throat can occur at 100 ppm, but at that concentration, there is no evidence of a decrease in pulmonary or central nervous system (CNS) function, nor is there evidence of injury or lasting effects (Ferguson et al. 1977). Adaptation to the odor and to the effects of ammonia at low concentrations (<100 ppm) has been demonstrated in occupational exposure studies of workers who were able to carry out job-related functions during extended periods of exposure (Vigliani and Zurlo 1955; Ferguson et al. 1977).

Ammonia is a colorless gas with a distinctive, penetrating, pungent odor that is often described as "drying urine." Exposure to ammonia vapor can cause symptoms that range from mild eye and throat irritation at low concentrations to severe respiratory injury and death at high concentrations. Ammonia is highly soluble in water, forming ammonium hydroxide through an exothermic reaction (Budavari et al. 1996). Exothermic reaction of ammonia with water can cause thermal and chemical burns because of the alkalinity of ammonium hydroxide. Contact with refrigerated liquid ammonia can cause cryogenic skin injury (Hathaway et al. 1991). In addition to being a potent respiratory irritant, ammonia is a potent ocular irritant, and it can rapidly penetrate the corneal epithelium. Severe ocular exposures can lead to corneal ulceration, corneal perforations, and persistent corneal opacity (NRC 1979).

Heating ammonia to decomposition produces ammonia vapor, hydrogen gas, nitrogen gas, and oxides of nitrogen (OSHA 1992; Sax and Lewis 1987). Under some conditions, mixtures of ammonia and air will explode when ignited, and fires and explosions can occur upon mixing of ammonia with other chemicals, such as chlorine, hypochlorites, and chlorine bleach (OSHA 1992). The National Fire Protection Association has assigned the flammability rating of 1 (slight fire hazard) to ammonia (New Jersey Department of Health 1998). The chemical and physical properties of ammonia are shown in Table 2–1.

Ammonia is found in the environment as the result of natural and industrial processes. It is released into the environment by the breakdown of organic wastes, and it is a constituent of the soil, the atmosphere, and bodies of water. Ammonia is also a key intermediate in the nitrogen cycle and is a product of amino acid metabolism (WHO 1986). Anhydrous ammonia is used in the production of nitric acid, explosives, synthetic fibers, and fertilizers (Budavari 1989). It is used as a refrigerant; as a corrosion inhibitor; in the purification of water supplies; in steel production; as a catalyst for polymers; as a preservative for latex; and in the production of nitrocellulose, urea formaldehyde, sulfite cooking liquors, and nitroparaffins (ACGIH 1991; Lewis 1993). Ammonium hydroxide (10–35% ammonia) is a major constituent of many cleaning solutions. Ammonia

is a potential combustion product of fires on disabled submarines. Examples of materials that can produce ammonia gas upon pyrolysis include wool, polyacrylonitrile, synthetic fabrics, and insulating foams (Hilado et al. 1977).

TABLE 2–1 Chemical and Physical Properties

CAS number	7664–41–7
Molecular formula	NH_3
Molecular weight	17.03
Color	Colorless
Odor	Pungent
Odor threshold	5–53 ppm
Boiling point	–33.35°C
Melting point	–77.7°C
Gas density	0.7714 g/L
Vapor density	0.5967 (air=1)
Solubility	Water, alcohol, chloroform, ether
Conversion factors at 25°C at 760 mm Hg	1 mg/m^3=1.41 ppm; 1 ppm=0.708 mg/m^3

Abbreviations: g/L, grams per liter; mg/m^3, milligrams per cubic meter; ppm, parts per million. Sources: Budavari (1989), ACGIH (1991), Hathaway et al. (1991).

TOXICOKINETIC CONSIDERATIONS

Absorption

Short-term inhalation studies (<2 min) in human volunteers have demonstrated that ammonia is almost completely retained (83–92%) in the nasal mucosa (Landahl and Herrmann 1950). With longer exposures (500 ppm for 30 min), retention of ammonia in the nasal mucosa decreases progressively until reaching equilibrium at 23% (range: 4–30%) after 10–27 min of exposure (Silverman et al. 1949). The authors reported that the concentration of ammonia in exhaled air remained stable after this period and returned to pre-exposure levels within 3–8 min after the exposure. Localized irritation in the nose and pharynx was further

evidence that ammonia is absorbed primarily in the upper respiratory tract. There was no evidence in this same study of lower airway irritation nor was there a significant increase in urine or blood ammonia concentrations or urea and nonprotein nitrogen concentrations.

Studies with laboratory animals support that conclusion. Egle (1973) exposed male and female mongrel dogs to ammonia at concentrations of 214–714 ppm. Retention in the whole respiratory tract ranged from 73% to 83%, and was not affected by concentration, respiratory rate, or tidal volume. When the lower and upper respiratory tracts were studied separately, retention was found to be approximately 78% in each.

In a study using rats, Schaerdel et al. (1983) exposed 4 groups of animals to ammonia at concentrations of 15, 32, 310, or 1,157 ppm for 24 h. Blood samples were taken 0, 8, 12, and 24 h after exposure. A significant increase in blood ammonia was found at the two highest concentrations after 8 h, but the increase was less marked at 12 or 24 h, suggesting an increase in ammonia metabolism. In another study, female rabbits were exposed to ammonia at concentrations of 50 or 100 ppm for 2.5–3 h (Mayan and Merilan 1972). No increase in blood pH was found, but there was a significant increase in blood urea nitrogen (BUN) in rabbits exposed to 100 ppm. In a study that exposed male Holstein calves to ammonia at concentrations of 50 and 100 ppm for 2.5 h, there was no increase in BUN or pH (Mayan and Merilan 1976).

No animal or human studies were located on the quantitative absorption of ammonia through the skin. However, dermal toxicity studies indicate that little or no ammonia is absorbed into the blood through the skin. Ammonia can rapidly penetrate the corneal epithelium (NRC 1979).

Distribution

Ammonia is normally present in all tissues of the body. The distribution and metabolic fate of absorbed ammonia depends on the route of administration. The distribution of endogenous and absorbed ammonia in various body compartments is influenced by pH. The lower the pH of a compartment, the greater its total ammonia content (NRC 1979). The normal concentration of ammonia in human blood is approximately 1 milligram per liter (mg/L) (Wands 1981). Total ammonia concentrations in humans are 70–113 micromoles (μmol) in arterial blood and plasma, 5–40 μmol in venous blood and plasma, and 20–100 μmol in cerebrospinal fluid (Cooper and Plum 1987).

No quantitative studies were available on the distribution of ammonia after inhalation. Inhaled ammonia is mostly absorbed in the upper respiratory tract;

only a small amount is absorbed into the systemic circulation. Silverman et al. (1949) demonstrated that when human subjects were exposed to 500 ppm for 30 min there was no effect on blood nitrogen concentrations. In contrast, Kustov (1967) demonstrated a significant increase in BUN in human subjects exposed to 20 ppm for 8 h. It is likely that exogenous ammonia absorbed into the blood would be processed similarly to endogenously produced ammonia (excreted in the urine, converted to glutamine and urea, used in protein synthesis).

Metabolism

Ammonia is formed as a product of protein and amino acid metabolism, and the rapid metabolism of ammonia in the liver maintains the isotonic system (Pierce 1994; Visek 1972). In humans, approximately 50 milligrams per kilogram (mg/kg) of ammonia is produced in the body each day from the metabolism of dietary protein and amino acids (ATSDR 1990). No studies were available on the metabolism of ammonia after inhalation or dermal exposure. Ingested ammonia is metabolized to urea and glutamine, primarily in the liver (Fürst et al. 1969; Pitts 1971), but it also can be converted to glutamine in the brain (Takagaki et al. 1961; Warren and Schenker 1964). The route of exposure affects the metabolism of ammonia. It is almost completely converted by the liver to urea after oral exposure, but it is metabolized in body tissues to glutamine or tissue protein after intraperitoneal and subcutaneous administration (Duda and Handler 1958; Fürst et al. 1969; Vitti et al. 1964). The nitrogen fixed in glutamine is eventually used in protein synthesis (Duda and Handler 1958; Fürst et al. 1969; Vitti et al. 1964). Duda and Handler (1958) administered ^{15}N-labeled ammonium acetate intravenously at a dose of 0.03 mg/kg to rats. Approximately 90% of the administered dose was converted to glutamine and urea within 30 min. Glutamine was the major early product. The investigators detected labeled nitrogen in amino acids, purines, pyrimidines, and other nitrogenous compounds.

Saul and Archer (1984) demonstrated that ammonia is oxidized to nitrate in the rat. Three male Sprague-Dawley rats were administered ^{15}N-labeled ammonium chloride by gavage at a dose of 1,000 μmol for 5 d. A significant amount (0.28±0.03 μmol, mean ± SE) of excess ^{15}N-labeled nitrate was found in the urine.

Because the CNS is sensitive to ammonia, its metabolism in the brain and the neurotoxicity associated with hyperammonia and hepatic encephalopathy (the proximate source of damage in the latter is also ammonia) is reviewed here. Hepatic encephalopathy (HE) or congenital and acquired hyperammonemia result in excessive ammonia accumulation within the CNS. The condition is due

to liver failure. Experimental studies in vivo have shown that the effects of ammonia on the CNS vary with its concentration. High concentrations within the CNS produced seizures, resulting from its depolarizing action on cell membranes; lower concentrations produced stupor and coma, consistent with its hyperpolarizing effects.

Ammonia intoxication is commonly associated with astrocytic swelling. In addition, astrocytes undergo morphologic changes following chronic exposure to ammonia, yielding the so-called Alzheimer type II astrocytes common to most hyperammonemic conditions. Notably, the astrocytic changes precede any other morphologic change in the CNS (Norenberg 1981). The exclusive site for the detoxification of glutamate to glutamine occurs within the astrocytes. This process requires adenosine-triphosphate-dependent amidation of glutamate to glutamine, a process mediated by the astrocyte-specific enzyme, glutamine synthetase (Norenberg and Martinez-Hernandez 1979). In vivo chronic exposure to ammonia leads to diminished glutamine metabolism within the astrocytes and to impairment of astrocytic energy metabolism (Albrecht 1996). It has been reported that the reduced astrocytic capacity to metabolize ammonia leads to ammonia-induced cytotoxicity in juxtaposed neurons, promoting accumulation of glutamine. This accumulation leads to decreased cerebral glucose consumption and amino acid imbalances (Hawkins and Jessy 1991; Hawkins et al. 1993). Increased intracellular ammonia concentrations also have been implicated in the inhibition of neuronal glutamate precursor synthesis, resulting in diminished glutamatergic neurotransmission, changes in neurotransmitter (glutamate) uptake, and changes in receptor-mediated metabolic responses of astrocytes to neuronal signals (Albrecht 1996).

Elimination

When absorbed into the systemic circulation, ammonia is primarily excreted by the kidney as urea and urinary ammonium compounds (Gay et al. 1969; Pitts 1971). Absorbed ammonia also can be excreted as urea in feces (Richards et al. 1975) and as a perspiration constituent (Guyton 1981; Wands 1981). In a study of male subjects exposed to ammonia at concentrations up to 500 ppm for 30 min, Silverman et al. (1949) found that 70–80% of inhaled ammonia was excreted in expired air. Ammonia in expired air returned to normal concentrations within 3 to 8 min after exposure was stopped. The investigators calculated that if all the retained ammonia were absorbed into the blood, there would be no significant change in blood or urine urea, ammonia, or nonprotein nitrogen.

HUMAN TOXICITY DATA

Experimental Studies

Henderson and Haggard (1943) reviewed the early data on ammonia exposure in humans, primarily that of Flurry and Zernick (1931) and Lehmann (1886), and reported responses to various concentrations of ammonia as listed in Table 2–2.

Pierce (1994) reported the odor threshold for ammonia can range from 5 to 53 ppm. Pedersen and Selig (1989) presented a summary of literature on human response to gaseous ammonia as presented by Markham (1986) (Table 2–3).

Mild and reversible effects of inhaling ammonia have been documented in several studies of human subjects exposed to ammonia at various concentrations and durations. Those studies are outlined in Table 2–4. Industrial Bio-Test Laboratories, Inc. (1973, cited in WHO 1986), determined the irritation threshold in ten human volunteers exposed to ammonia at concentrations of 32, 50, 72, or 134 ppm for 5 min. Irritation was defined as any discomfort in the nose, throat, eyes, mouth, or chest. The subjects showed dose-related responses for chest irritation and dryness of the eye, nose, and throat. The severity of the effects was not noted.

MacEwen et al. (1970) studied the effect of head-only exposure to ammonia at concentrations of 30 and 50 ppm for 10 min in six human volunteers. Each subject rated irritation responses on a scale of 0 to 4 (not detectable, just perceptible, moderate irritation, discomforting or painful, exceedingly painful) and odor perception on a scale of 0 to 5 (not detectable, positively perceptible, readily perceptible, moderate intensity, highly penetrating, and intense or very strong). At 30 ppm, three subjects reported irritation as not detectable, two subjects reported the irritation as just perceptible, and one subject gave no response. At 30 ppm, the odor was highly penetrating for three subjects, and moderately

TABLE 2–2 Ammonia Exposure in Humans

Concentration (ppm)	Effect
53	Least detectable odor
408	Lowest concentration causing throat irritation
698	Lowest concentration causing ocular irritation
1,720	Lowest concentration that caused coughing
2,000–6,500	Dangerous for short (0.5 h) exposures
5,000–10,000	Rapidly fatal for short exposures

Source: Adapted from Henderson and Haggard (1943).

intense for two subjects. The sixth subject gave no response. At 50 ppm, four subjects reported the irritation as moderate, one as just perceptible, and one as not detectable. The odor was highly penetrating or intense for all six subjects inhaling 50 ppm of ammonia.

TABLE 2–3 Human Response to Gaseous Ammonia

Concentration (ppm)	Exposure time (min)	Effect
72	5	Some irritation
330	30	Concentration tolerated
600	1–3	Eyes streaming within 30 s
1,000	1–3	Eyes streaming immediately; Vision impaired but not lost; Breathing intolerable to most
1,500	1–3	Instant reaction is to escape

Source: Adapted from Pederson and Selig (1989).

Silverman et al. (1949) measured responses from six healthy human subjects in response to 30-min exposures to 500 ppm and from one subject exposed to 500 ppm for 15 min. The subjects hyperventilated and reported decreased sensitivity of the skin around the nose and mouth that disappeared soon after the end of the exposure. Two subjects reported irritation of the nose and throat starting at the beginning of the exposure and lasting 24 h. The irritation reported was likened to persistent nasal stuffiness. Two subjects were able to continue nasal breathing throughout the 30 min; the others changed to mouth breathing. There was no difference in the effects noted in the subject inhaling ammonia for 15 min and those inhaling ammonia for 30 min.

Ferguson et al. (1977) reported that some industrial workers did not voluntarily use gas masks until ammonia concentrations reached 400 or 500 ppm in the workplace. The authors also reported that, before 1951, workers were routinely subjected to continuous workplace concentrations ranging from 150 to 200 ppm. In an effort to measure the responses of human subjects to concentrations of ammonia reportedly often encountered in industrial settings, three groups of two subjects each were exposed at 25, 50, and 100 ppm ammonia for 6 h/d, 5 d/wk, for 6 weeks. These exposures followed exposure to the same concentrations for a 1-wk practice period. Observations were made of irritation to the conjunctiva of the eyes and mucous membranes of the nose and throat. Vital signs (pulse, blood pressure, respiratory rate) were measured, as were parameters of pulmonary function. With exposures up to 100 ppm there were no significant differences between experimental and control subjects in the parameters measured. The authors further demonstrated that after a period of acclimation, exposures

to ammonia at up to 100 ppm produced no increase in observed or reported irritation. The only complaints were lacrimation and nasal dryness during brief excursions above 150 ppm. Transient exposures of subjects to 200 ppm produced temporary discomfort with no lasting health effects. These workers were able to perform tasks during the exposure and carried out their daily operations in the workplace without consequence from the experimental exposures.

In another study designed to establish limits of exposure and to examine adaptation to ammonia, Verberk (1977) exposed 16 healthy subjects to 50, 80, 110, and 140 ppm for 2 h. None of the subjects had previously been exposed to ammonia in experiments or at work; however, eight subjects (“expert” group) had experience in toxicology and were aware of the effects of ammonia exposure. Pulmonary function was measured, as were subjective assessments of irritation and discomfort parameters (irritation of eyes, throat, tightness of chest, urge to cough, tolerance to odor). There were no effects on lung function in any exposed individual at the concentrations used. Many subjects reported increases in subjective measures at the higher concentrations, with a non-expert group rating its effects as more severe. At 140 ppm, none of the non-expert group remained in the exposure chamber for the entire 2-h period, whereas all of the expert subjects remained for the entire exposure period. The greatest difference in responses between the expert and non-expert groups was in general discomfort. The expert group perceived no general discomfort even after exposure to the highest concentration for 2 h, whereas the non-expert subjects perceived general discomfort that ranged from “distinctly perceptible” to “unbearable” after 1 h. There were no differences detected between smokers and nonsmokers. No subjects were considered to be hypersensitive to nonspecific irritants. Cole et al. (1977) studied the effect of ammonia exposure in 18 subjects exposed to concentrations of 101, 151, 206, and 336 ppm for brief periods before and during exercise. Statistically significant decreases in minute volume and exercise tidal volume were detected at 151 ppm and above; respiratory frequency was increased at 206 ppm and above.

Holness et al. (1989) compared effects in a group of 58 workers chronically exposed to ammonia vapor (9.2±1.4 ppm, mean ± standard deviation) with the effects in a group of plant workers who had no exposure to ammonia (0.3±0.1 ppm, mean ± standard deviation). During a 1-wk period, the workers were assessed, based on a questionnaire, on sense of smell and respiratory function. There were no reported differences between the two groups.

Erskine et al. (1993) measured the threshold concentration of ammonia required to elicit reflex glottis closure, which is a protective response stimulated by inhaling irritant or noxious vapors at concentrations too small to produce cough. Glottis closure was measured in 102 healthy nonsmoking subjects between the ages of 17 and 96. The results showed a strong correlation between age

TABLE 2-4 Human Toxicity Data, Experimental Exposure to Ammonia

Subjects	Route	Concentration (ppm)	Duration	Effect	Reference
EXPERIMENTAL STUDIES					
10 healthy volunteers	Whole body	32, 50, 72, 134	5 min	32 ppm : 1 reported dryness of the nose. 50 ppm: 2 reported dryness of the nose. 72 ppm: 3 reported eye irritation; 2 reported nasal irritation; 3 reported throat irritation. 134 ppm: 5 reported eye irritation; 7 reported nasal irritation; 8 reported throat irritation; 1 reported chest irritation	Industrial Bio-Test Laboratories, Inc. 1973 (as cited in WHO 1986)
6 healthy volunteers	Whole body	30, 50	10 min	At 50 ppm: 4 subjects reported moderate irritation; but none found that concentration to be discomforting or painful.	MacEwen et al. 1970 (as cited in WHO 1986)
7 healthy volunteers	Inhalation	500	30 min	All of the subjects exhibited an increase in respiratory rate and minute volumes. Hyperventilation occurred immediately in 3 subjects, and after 10-30 min in 4 subjects. Respiratory minute volumes were 50-250% greater than control values, and exhibited a cyclic variation, decreasing by about 25% at 4-7 min intervals. Subjects reported nose and throat irritation, hypesthesia (decreased sensitivity to simulation) of the skin of the nose and mouth.	Silverman et al. 1949
16 healthy volunteers	Whole body	50, 80, 110, 140	2 h	Subjects were divided into 8 "experts" (familiar with the effects of ammonia) and 8 "non-experts" (unfamiliar with effects).	Verberk 1977

Subjects	Route	Concentration (ppm)	Duration	Effect	Reference
				Effects on respiratory function were measured by vital capacity, forced inspiratory volume, and forced expiratory volume immediately after exposure; subjective responses were taken at 15-min intervals. No effects on respiratory function were found. Subjects reported irritation of the eyes and throat, objectionable odor, and general discomfort. Non-experts rated their effects as more severe than did the experts. At the highest concentration, none of non-experts stayed in exposure chamber for 2 h; all of the experts remained in the chamber.	
6 workers	Whole body	25, 50, 100	2-6 h/d; 5 d/wk for 6 wk	In 3 groups of 2 workers each, no effects observed on the eyes, nose, throat, pulse rate, respiratory function (under either normal or exercise conditions). No effects on physical or mental ability to perform work duties. Subjective responses were lacrimation and dryness of the nose and throat at 150-200 ppm. (In some tests in the exposure chamber, concentration rose briefly to 200 ppm.)	Ferguson et al. 1977
18 volunteers under exercise conditions	Whole body	101, 151, 206, 336	9 min pre-exposure; 8-11 min during exercise	Respiratory effects measured by respiratory rate, minute volume, tidal volume, oxygen uptake. Statistically significant decrease in ventilation minute volume and exercise tidal volume at 151 and 206 ppm, respiratory frequency increased at 206 and 336 ppm.	Cole et al. 1977

and the threshold concentration. The younger subjects were more sensitive, with the reflex response occurring at 571 ppm in subjects aged 21–30 and at 1,791 ppm in subjects aged 86–95. The threshold was about 1,000 ppm for 60-yr-old subjects. The decreased reflex activity of the glottis suggests that protection of the airways in elderly people could be less than that of much younger people.

Collectively, these studies show that ammonia at concentrations as high as 140 ppm has no effect on pulmonary function, but it causes irritation of the eyes, nose, and throat at concentrations as low as 72 ppm. Those studies provide the critical data on which to base both SEAL 1 and SEAL 2.

Accidental Exposures

Table 2–5 presents the details of studies related to accidental exposures to ammonia. All studies involved inhalation and dermal exposure to ammonia at high concentrations, although it was not possible to quantify them. Accidental exposure has resulted in both immediate and delayed mortality (Caplin 1941; Hoeffler et al. 1982; Mulder and Van der Zalm 1967; Sobonya 1977). Other exposure cases have resulted in injury to the respiratory tract, including mild to severe irritation, tracheal and bronchial burns, and airway obstruction (Close et al. 1980; Sobonya 1977; Walton 1973); burns or irritation to the skin, eyes, and mucous membranes of the nasal and oral passages (Hatton et al. 1979; Mulder and Van der Zalm 1967); and cardiac effects (Hatton et al. 1979; Montague and Macniel 1980). Hematological and musculoskeletal effects have also been documented (White 1971). In cases of severe exposure, respiratory effects can persist for years (Levy et al. 1964; Kass et al. 1972; Flury et al. 1983; Leduc et al. 1992). The respiratory dysfunction caused by acute high-level ammonia exposure can be biphasic: Immediate effects can lead to severe pulmonary damage, edema, and death. But if there is initial recovery, secondary effects can lead to death or debilitating chronic respiratory disease (Dodd and Gross 1980). Because of the high concentrations of ammonia exposure, further discussion of these case reports is of limited usefulness in deriving either SEAL 1 or SEAL 2.

Occupational and Epidemiologic Studies

Table 2–6 provides details of occupational and epidemiologic studies of workers exposed to ammonia. Overall, differences were found in pulmonary function among workers exposed to ammonia compared with non-exposed workers. Some studies reported increased subjective reports of respiratory, dermal, or ocular irritation, but it is unclear whether these effects can be attrib

TABLE 2-5 Human Toxicity Data, Accidental Exposure to Ammonia

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
6 ice cream factory workers	Whole body	NR	NR	Subjects exhibited shock, acute inflammation of the respiratory tract, and burns to the skin and eyes. One subject died 1 mo after exposure; autopsy revealed acute laryngo-tracheitis, tracheobronchitis, and bronchopneumonia.	Slot 1938
1 worker	Whole body	NR	NR	Death by cardiac arrest 6 h after exposure; autopsy revealed marked respiratory irritation, denudation of tracheal epithelium, pulmonary edema. Before death, effects included coughing dyspnea, vomiting, reddened and swollen face, red and raw mouth and throat, conjunctivitis.	Mulder and Van der Zalm 1967 (as cited in NIOSH 1974)
7 workers	Whole body	NR	NR	1 death; autopsy and histologic examination revealed obstructed airway, acute congestion and edema of the lungs, denudation of the bronchial epithelium, red blood cells and edema fluid in the alveoli. Survivors suffered burns of the mucous membranes, skin, and eyes; difficulty breathing. Airway damage and reduced gas transfer observed for up to 3 yr after exposure.	Walton 1973

47 subjects	Whole body	NR	NR	Subjects classified as "mildly," "moderately," or "severely" affected. Mildly affected: No deaths among 9 subjects; acute pharyngitis and tracheitis. Moderately affected: 6 of 27 died; 3 subjects exhibited symptoms similar to pulmonary edema and died within 36 h; 9 subjects developed bronchopneumonia within 2-3 d and 3 died 2 d after onset. Severely affected: 7 of 11 died; all subjects had pulmonary edema, and 7 died within 48 h.	Caplin 1941
1 worker	Whole body	NR	NR	Immediate effects included bilateral conjunctival edema; respiratory distress, wheezing, rhonchi, rales; skin burns; pulmonary edema. Subject died 60 d after exposure. Autopsy revealed bronchiectasis, fibrous obliteration of small airways, terminal nocardial pneumonia, mucous plugging and mural thickening of the smallest bronchi and some bronchioles.	Sobonya 1977
1 subject	Whole body	NR	NR	Female exposed in trucking accident died 3 yr after exposure. She suffered from severe respiratory effects (pulmonary edema) immediately after exposure and required mechanical-assisted respiration until death. Autopsy revealed bronchiectasis and bacterial bronchitis.	Hoeffler et al. 1982

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
2 subjects	Whole body	NR	NR	Both subjects died of acute ammonia exposure; light microscopy of pulmonary tissues revealed denudation of tracheobronchial epithelium; edema of lamina propria; and marked alveolar edema, congestion, and hemorrhage. Electron microscopy of tissues showed marked swelling and imbitional edema of Type I alveolar epithelial cells, no effect on alveolar basement membranes and capillary endothelial cells.	Burns et al. 1985
9 subjects	Whole body	NR	NR	Subjects divided into 2 groups: Those exposed to high concentrations over a short period (n = 3) and those exposed to lower concentrations over a prolonged period (n = 6). One highly exposed individual died, and the other 2 had upper airway obstruction that necessitated early intubation or tracheostomy, burns to the skin and mucous membranes of the upper airway, and epithelial defects of the cornea; Individuals recovered with few respiratory sequelae. Subjects who experienced longer-term exposure had burns of the face, eyes, and	Close et al. 1980

				skin; had burns of the upper respiratory tract. None had upper airway obstruction but did suffer long-term pulmonary sequelae.	
1 subject	Whole body	NR	3 min	Immediate effects included burns of the face, eyes, and oral cavity. Subject developed clinical and radiologic features of pulmonary edema, respiratory failure with tachypnoea and arterial hypoxaemia, airflow obstruction. Death occurred 12 wk after exposure. Autopsy revealed bronchiectasis and obliterative bronchiolitis.	Price et al. 1983
4 subjects	Whole body	NR	NR	Upper airway obstruction; second- or third-degree burns to the skin; burns or irritation of the mouth, nose, throat, eyes; some pulmonary damage. One subject (6 mo) suffered cardiorespiratory arrest). All recovered between 7 and 32 d.	Hatton et al. 1979
14 fishermen	Whole body	NR	NR	Respiratory distress, pharyngeal or pleuritic chest pain, cough, dyspnea, ocular irritation. Some exhibited tachypnea, rales, rhonchi, wheezing, tachycardia.	Montague and Macneil 1980
1 subject	Whole body	NR	NR	Loss of consciousness; rapid and heavy respiration; burns on the neck, eyes, skin; elevated blood pressure and pulse; lungs with fine and harsh rales; spastic extremities; increased white blood cell count.	White 1971

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
8 subjects	Whole body	NR	NR	Immediate effects included eye and throat irritation, difficulty breathing. Some had burns of the skin, tachycardia, tachypnoea. Severely affected subjects showed evidence of impaired pulmonary function up to 2 yr after exposure.	Ward et al. 1983
1 subject	Whole body	NR	NR	Male subject splashed with liquid ammonia suffered burns of the skin and upper airway obstruction. Follow-up examinations for 5 yr indicate persistent central and peripheral airway obstruction.	Flury et al. 1983
8 workers	Whole body	NR	NR	Subjects described as having "mild," "moderate," and "heavy" exposure. Mildly exposed subjects had burns of the oral cavity, pharynx, eyes. Moderately exposed subjects exhibited bronchospasm, labored breathing, transient bilateral rhonchi. Heavily exposed subjects severe irritation of the eyes, oral cavity, pharynx; inspiratory and expiratory rhonchi. 1 subject needed mechanical ventilation and tracheostomy.	O'Kane 1983
1 subject	Whole body	NR	NR	Immediate effects included burns of the respiratory tract, eyes, skin; dyspnea; labored breathing. Tubular bronchiectasis 8 yr after the accident. Airflow obstruction, cough, frequent bronchial infections, dyspnea upon	Leduc et al. 1992

				exertion persisted for 12 yr after exposure.	
2 subjects	Whole body	NR	30, 90 min	Immediate effect included burns of the respiratory tract, eyes, skin. Both suffered from residual effects more than 2 yr after exposure. Effects included bronchiectasis, visual deterioration, small airway obstruction, atelectasis, emphysema in the lungs; thickened alveolar walls with histiocytic infiltration into alveolar spaces,; mucous and desquaminated cells in the bronchiolar lumen.	Kass et al. 1972
1 subject	Whole body	NR	NR	Irritation of the eyes, dyspnea, pharyngeal edema, and bilateral diffuse rhonchi and rales. 2 yr after exposure, subject needed traceostomy and mechanical ventilation, eventually permanent traceostomy.	Stroud 1981
4 subjects	Whole body	NR	NR	Subjects sprayed on the face and upper body with liquid ammonia had upper airway obstruction, burns to the skin, mucous membranes of the oral cavity and pharynx, and eyes.	Levy et al. 1964

TABLE 2-6 Human Toxicity Data, Occupational and Epidemiology Studies of Exposure to Ammonia

Subjects	Route	Concentration, ppm	Duration	Effect	Reference
Workers	Whole body	20-100	NR	Irritation of the upper respiratory tract, eyes. Workers accustomed to 20 ppm showed redness of the conjuctiva but did not report irritation; unaccustomed workers reported irritation. No other details provided. No information on methods used to survey workers.	Vigliani and Zurlo 1955 (as cited in NIOSH 1974)
73 workers in ammonia production plant	Whole body	13-51	NR	Exposed workers reported more headaches, vertigo, staggering, and tremors. Unclear whether effects can be attributed solely to ammonia, because the workers were exposed to other compounds and because of possible selection and/or reporting bias.	Kirhov 1977 (as cited in Swotinsky and Chase 1990)
41 workers in ice-manufacturing plant	Whole body	NR	NR	Questionnaires administered before and after work shifts were compared with those from 28 nonexposed workers. Chronic bronchitis was found in 20% of exposed workers and 14% of nonexposed workers. No differences between the groups in ventilatory function tests or chest examinations.	el-Sewefy and Awad 1971 (as cited in NRC 1987)
8 workers in blueprint shop	Whole body	4-29	NR	Ocular irritation reported in an unspecified number of workers.	Mangold 1971 (as cited in NIOSH 1974)

58 sodium carbonate industry workers	Whole body	9.2 ± 1.4 (mean ± SD)	12.2 yr	Workers exposed during production of sodium carbonate compared with 31 control workers (mean concentration, 0.3 ± 0.1 ppm). Investigators assessed subjective respiratory, ocular, dermal responses; sense of smell; baseline lung function at the beginning and end of a work week; changes in lung function over a work shift. No significant differences between the exposure groups, no relationship found between concentration or length of ammonia exposure and lung function.	Holness et al. 1989

Abbreviations: SD, standard deviation; NR, not reported.

uted solely to ammonia. Some of the studies were poorly conducted or documented, and co-exposures to other chemicals often were involved.

TABLE 2–7 LC50 for Exposure to Ammonia

Species	Duration	LC_{50} (ppm)	Reference
Rat	10 min	40,300	Appelman et al. 1982
	15 min	17,401	Prokop'eva et al. 1973 (as cited in ATSDR 1990)
	20 min	28,595	Appelman et al. 1982
	40 min	20,300	Appelman et al. 1982
	60 min	16,600	Appelman et al. 1982
	60 min	7,338	MacEwen and Vernot 1972 (as cited in WHO 1986)
	960 min	1,000	Weedon et al. 1940 (as cited in ATSDR 1990)
Mouse	10 min	9,960	Silver and McGrath 1948
	30 min	21,430	Hilado et al. 1977
	60 min	4,837	MacEwen and Vernot 1972 (as cited in WHO 1986)
	60 min	4,230	Kapeghian et al. 1982
	960 min	1,000	Weedon et al. 1940 (as cited in ATSDR 1990)
Rabbit	60 min	9,870	Boyd et al. 1944
Cat	60 min	9,870	Boyd et al. 1944

Abbreviation: LC_{50}, median lethal concentration.

EXPERIMENTAL ANIMAL TOXICITY DATA

Acute inhalation experiments with ammonia have demonstrated lethal and nonlethal toxic effects in a variety of laboratory animals. Table 2–7 lists LC_{50} (the concentration that is lethal to 50% of test animals) reported for ammonia in various species. Mice are particularly sensitive to ammonia and other irritant gasses (Alarie 1973; Alarie 1981; Kapeghian et al. 1982).

Of particular relevance is the work of Buckley et al. (1984). Respiratory lesions induced by sensory irritants were compared in mice exposed at RD_{50} (the

concentration that causes a 50% decrease in respiratory rate). In this study, the effects of exposure to the RD_{50} concentrations for ammonia (303 ppm) and hydrogen chloride (309 ppm) were compared (Barrow et al. 1978). Even though hydrogen chloride and ammonia have similar water solubility and RD_{50} values, the injury caused by hydrogen chloride was extensive, whereas there were no observable histopathologic changes in the respiratory tracts of mice exposed to ammonia at 303 ppm. Thus, in the case of ammonia, significant irritation does not necessarily translate into pathology. Studies in rabbits also indicate that because of its water solubility, ammonia is absorbed by the mucous coating of the upper respiratory tract, thus reducing exposure to the lower respiratory tract. For example, Boyd et al. (1944) reported less toxic effects (e.g., damage to trachea, effects on bronchioles) in rabbits exposed to ammonia inhaled through the nose and mouth compared with rabbits whose exposures were directly into the trachea. Table 2–8 describes acute animal toxicity studies with ammonia.

Repeated or continuous exposure over several days or weeks has been studied in several animal species. The details of those studies are also presented in Table 2–8. As in acute studies, the primary effects caused by exposure are irritation of the upper respiratory tract, eyes, and skin. The results of the study by Buckley et al. (1984) are supported by the work by Zissu (1995), who repeatedly exposed mice to various concentrations of ammonia 6 h/d for up to 14 d. The minimum concentration of ammonia causing histopathologic changes in respiratory epithelium was 711 ppm. No changes were seen in the olfactory epithelium, lung, or trachea at this concentration.

Some studies indicate that ammonia can increase susceptibility to pathogens (Anderson et al. 1964; Broderson et al. 1976; Schoeb et al. 1982; Targowski et al. 1984) and could affect behavior (Tepper et al. 1985). There are no animal toxicity studies specifically on dermal exposure to ammonia gas, but most of the inhalation studies outlined in Table 2–8 involved whole body exposures. Those studies report burns and irritation of the skin, eyes, and mucous membranes of the upper respiratory system. In general, the severity of the damage is related to the concentration and duration of exposure.

OTHER CONSIDERATIONS

Mechanism of Action

Ammonia is an irritant gas that produces effects immediately upon contact with moist mucous surfaces of the eyes and respiratory tract via the formation of ammonium hydroxide and the production of heat (NRC 1994). Because of its offensive odor and irritant properties, a person who is exposed to ammonia

TABLE 2-8 Experimental Animal Toxicity Data, Exposure to Ammonia

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
ACUTE EXPOSURE						
Rat: 2-3	Inhalation (mouth only)	10, 20, 45, 90	8 min	Ciliary movement in the trachea stopped in a concentration-dependent fashion.	LOAEL: 10	Dalhamn 1956
Rat: 10	Inhalation	13, 920-53, 330	10 min-1 h	Mortality was concentration related. LC_{50} significantly lower for males than females. Animals exhibited restlessness, nasal and eye irritation, dyspnea. Hemorrhagic lungs found in animals that died and those that survived.	NA	Appelman et al. 1982
Rat: 10	Inhalation	6,210, 7,820, 9,840	1 h	8 and 9 deaths in the mid- and high-concentration groups, respectively. Nasal and eye irritation, labored breathing in all groups. Surviving rats necropsied after 14 d exhibited fatty livers.	LOAEL: 6,210	MacEwen and Vernot 1972 (as cited in WHO 1986)
Rat: 3	Inhalation	100-300	6 h	Behavioral activity assessed by wheel running. At low concentration, free-access wheel running was decreased by 61%. At high concentration, activity ceased throughout exposure. Activity steadily increased after exposure stopped.	LOAEL: 100	Tepper et al. 1985

Rat: 8	Inhalation	15, 32, 310, 1,157	24 h	No significant effects.	NOAEL: 1,157	Schaerdel et al. 1983
Mouse: 20	Inhalation	8,600-12,690	10 min	25% of the mice died at the lowest concentration; 80% died at the highest concentration. Animals exhibited excitement, nasal and eye irritation, convulsions.	NA	Silver and McGrath 1948
Mouse: 4	Inhalation	303	30 min	50% reduction in respiratory rate.	NA	Barrow et al. 1978
Mouse: 4	Inhalation	7,143 - 28,571	30 min	4 deaths each at 26,190 ppm and 28,571 ppm; 3 deaths at 23,810 ppm; 2 deaths at 21,429 ppm; 1 death at 19,048 ppm. No deaths at 14,286 ppm and lower.	NA	Hilado et al. 1977
Mouse: 10	Inhalation	3,600, 4,550, 5,720	1 h	3 and 9 deaths in mid- and high-concentration groups, respectively. Nasal and eye irritation, dyspnea, convulsions. Surviving animals had lower body weight at 14 d. At necropsy, mild liver congestion found in mid- and high-concentration groups.	LOAEL: 3,600	MacEwen and Vernot 1972 (as cited in WHO 1986)
Mouse: 12	Inhalation	3,440-4,860	1 h	Significant number of deaths occurred at concentrations of 3,950 ppm and greater. No deaths occurred at 3,440 ppm and lower. Animals exhibited ataxia, tremors, convulsions, excited	LOAEL: 3,440	Kapeghian et al. 1982

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
				behavior, eye and nose irritation, dyspnea before death. Pathologic examination of dead animals showed acute vascular congestion, diffuse intraalveolar hemorrhage, congestion of hepatic sinusoids and blood vessels. Pathologic examination of surviving animals revealed mild to moderate chronic focal pneumonitis, focal atelectatic changes (high-concentration only), hepatic cellular damage.		
Chicken: 12	Inhalation	50	48 h	Exposure increased infection rate with Newcastle disease virus.	LOAEL: 50	Anderson et al. 1964
Chicken: 12	Inhalation	20	72 h	Exposure increased infection rate of chickens to Newcastle disease virus.	LOAEL: 20	Anderson et al. 1964
Rabbit: 8-17	Inhalation	9,870	1 h	Exposure occurred before or after intratracheal cannulation to collect respiratory tract fluid. Mean survival time was 18 h for animals exposed after cannulation and 33 h for those exposed before cannulation. Histopathologic changes were different in the groups: Animals exposed after cannulation had	NA	Boyd et al. 1944

				tracheal and bronchial damage; none of those effects were found in animals exposed before cannulation. Damage to the bronchioles and alveoli was similar in both groups.		
Rabbit: 7-9	Inhalation	50, 100	2.5-3 h	Respiratory rate decreased 34% and 32%, respectively. No histopathologic changes in lunch, liver, spleen, kidneys.	LOAEL: 50	Mayan and Merilan 1972
Cat: 4-5	Inhalation (endo-tracheal tube)	1,000	10 min	Severe dyspnea, anorexia, dehydration, bronchial breath sounds, sonorous and sibulent ronchi, coarse rales. Pulmonary function tests indicated increased pulmonary resistance throughout the study and significantly increased functional residual capacity on day 21. At necropsy, lungs were congested, hemorrhagic, edematous; there was interstitial emphysema, collapse. Histopathologic changes included necrosis and sloughing of bronchial epithelium on day 1; healing of the bronchial epithelium was detected on day 7. On days 21 and 35, there was evidence of bronchitis, bronchiolitis, bronchopneumonia, bulbous emphysema, thought to be caused by opportunistic infections.	LOAEL: 1,000	Dodd and Gross 1980

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
REPEATED OR CONTINUOUS EXPOSURE						
Rat: 7	Inhalation	4, 24, 44, 165, 714	3-7 d	No significant effects in blood pH, blood gases, hepatic-drug-metabolizing enzyme activity. Histologic examination showed minor lesions of the respiratory epithelium in animals exposed for 7 d; no changes observed in trachea or lungs. The concentrations at which those lesions occurred was not specified.	NA	Schaerdel et al. 1983
Rat: 5	Inhalation	435	7 d	Trachea effects included inflammation, infiltration of neutrophils, large mononucleated cells, monocytes, immature fibroblasts.	LOAEL: 435	Gamble and Clough 1976
Rat: 5	Inhalation	200	4-12 d	Tracheal hyperplasia damage increased with duration.	LOAEL: 200	Gamble and Clough 1976
Rat: 5	Inhalation	25, 300	6 h/d, for 5-15 d	Metabolic acidosis observed at day 5 but not thereafter. No treatment-related effects observed in the lung, liver, kidney.	NOAEL: 300	Manninen et al. 1988
Rat: 12	Inhalation	250	35 d	No clinical symptoms observed. Pathologic examination revealed nasal lesions, predominantly in the anterior of the nasal passages. Histopathological	LOAEL: 250	Broderson et al. 1976

					changes included thickening of respiratory, olfactory epithelium. Cells along the basement membrane had pyknotic nuclei, eosinophilic cytoplasm.		
	Rat: 12	Inhalation	25, 50, 100, 250	35-49 d, continuous	Rats were inoculated with *Mycoplasma pulmonis* on day 7. Animals exposed to ammonia showed significantly increased symptoms of murine respiratory mycoplasmosis; severity of rhinitis, otitis media, tracheitis, pneumonia was increased. Pathologic and microscopic changes characteristic of infection also increased in exposed rats.	LOAEL: 25	Broderson et al. 1976
	Rat: 49	Inhalation	2, 100	4 wk, continuous	Pathogen-free rats inoculated with *M. pulmonis* and exposed to ammonia had greater bacterial growth and immunologic responses than unexposed inoculated rats. Effects were considered secondary to effects in the nasal passages.	LOAEL: 100	Schoeb et al. 1982
	Rat: 15	Inhalation	220, 1,090	8 h/d, 5 d/wk for 6 wk	Nonspecific inflammatory changes observed in the lungs of the 1,090 ppm group.	NOAEL: 220 LOAEL: 1,090	Coon et al. 1970
	Rat: 48-51	Inhalation	180, 370, 640	90 d, continuous	At 640 ppm, 50 of 51 rats died by day 65. Animals exhibited dyspnea and nasal irritation. No significant effects observed at the other concentrations.	NOAEL: 370	Coon et al. 1970

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Rat: 15	Inhalation	660	90 d, continuous	13 of 15 animals died. Histopathologic examination revealed focal or diffuse interstitial pneumonitis, calcification of renal tubules, calcification of bronchial epithelial, renal tubular epithelial proliferation, myocardial fibrosis; fatty changes of the liver in several animals. Changes were also found in control animals, but were of lesser severity.	LOAEL: 660	Coon et al. 1970
Rat: 15	Inhalation	60	114 d, continuous	No significant effects.	NOAEL: 60	Coon et al. 1970
Mouse: 16-24	Inhalation	303	6 h/d for 5 d	Histopathologic changes in respiratory epithelium of nasal cavity included minimal exfoliation, erosion, ulceration, necrosis; moderate inflammation; minimal squamous metaplasia. No lesions found in tracheobronical or pulmonary regions.	LOAEL: 303	Buckley et al. 1984
Mouse: 10	Inhalation	78, 257, 711	6 h/d for 4-14 d	No clinical signs of toxicity. Lesions of respiratory epithelium (rhinitis with metaplasia and necrosis) observed at highest concentration. Severity increased	NOAEL: 257 LOAEL: 711	Zissu et al. 1995

				with exposure duration. No lesions found in trachea or lungs.		
	Mouse: 20	Inhalation	20	6 wk, continuous	No clinical or pathologic effects observed up to 4 wk. At 6 wk, evidence of pulmonary edema, congestion, hemorrhage.	LOAEL: 20	Anderson et al. 1964
	Chicken: 12	Inhalation	1,000	2 wk	At 3 d, animals had photophobia and nasal secretion. At 8 d, corneal opacity evident. Pathologic examination at 2 wk revealed pulmonary congestion, edema, hemorrhage; congestion of liver and spleen.	LOAEL: 1,000	Anderson et al. 1964
	Chicken: 14	Inhalation	200	3 wk	Ocular irritation, increased mucous secretion, anorexia, weight loss observed between 1 and 2 wk. At 2-3 wk, lungs congested, edematous, and hemorrhagic; liver congested; and corneas slightly clouded.	LOAEL: 200	Anderson et al. 1964
	Chicken: 21	Inhalation	20	12 wk	No clinical or pathologic effects observed up to 4 wk. At 6 wk, lungs darkened, edematous, congested, hemorrhagic.	LOAEL: 20	Anderson et al. 1964
	Guinea pig: 8	Inhalation	50, 90	3 wk	No evidence of distress, ocular irritation, respiratory diseases, no effects on erythrocyte, leukocyte counts. Significant decrease in cell-mediated immune responses to challenge with a derivative of tuberculin at 90 ppm.	NOAEL: 50	Targowski et al. 1984

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Guinea pig: 15	Inhalation	220, 1,090	8 h/d, 5 d/wk for 6 wk	Nonspecific inflammatory changes observed in the lungs of the 1,090-ppm group.	NOAEL: 220 LOAEL: 1,090	Coon et al. 1970
Guinea pig: 10	Inhalation	20	6 wk, continuous	No clinical or pathologic effects observed up to 4 wk. At 6 wk, lungs darkened, edematous, congested, hemorrhagic.	LOAEL: 20	Anderson et al. 1964
Guinea pig: 6	Inhalation	50	6 wk, continuous	Grossly enlarged spleen; congested liver, spleen, lungs; pulmonary edema.	LOAEL: 50	Anderson et al. 1964
Guinea pig: 15	Inhalation	660	90 d, continuous	4 of 15 animals died. Histopathologic examination revealed focal or diffuse interstitial pneumonitis, calcification of renal tubules, calcification of bronchial epithelial, renal tubular epithelial proliferation, myocardial fibrosis, fatty changes of the liver in several animals. Changes also found in control animals, but of lesser severity.	LOAEL: 660	Coon et al. 1970
Guinea pig: 15	Inhalation	60	114 d, continuous	No significant effects.	NOAEL: 60	Coon et al. 1970

Guinea pig: NS	Inhalation	170	6 h/d, 5d/wk for 18 wk	No adverse effects up to 12 wk. At necropsy at 18 wk, mild changes observed in spleen, kidney suprarenal glands, livers. No effects found in lungs.	LOAEL: 170	Weatherby 1952 (as cited in IRIS)
Rabbit: 3	Inhalation	220, 1,090	8 h/d, 5 d/wk for 6 wk	Mild to moderate lacrimation and dyspnea during wk 1 in the 1,090-ppm group, disappeared during wk 2.	NOAEL: 1,090	Coon et al. 1970
Rabbit: 3	Inhalation	660	90 d, continuous	Marked eye irritation. At necropsy, moderate lung congestion in 2 rabbits. Histopathologic examination revealed focal or diffuse interstitial pneumonitis, calcification of renal tubules, calcification of bronchial epithelial, renal tubular epithelial proliferation, myocardial fibrosis, fatty changes of the liver in several animals. Changes also found in control animals, but of lesser severity.	LOAEL: 660	Coon et al. 1970
Rabbit: 3	Inhalation	60	114 d, continuous	No significant effects.	NOAEL: 60	Coon et al. 1970
Dog: 2	Inhalation	220, 1,090	8 h/d, 5 d/wk for 6 wk	Mild to moderate lacrimation and dyspnea during wk 1 in 1,090 ppm group, but disappeared during wk 2.	NOAEL: 1,090	Coon et al. 1970

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Dog: 2	Inhalation	660	90 d, continuous	Marked eye irritation and nasal discharge. 1 of 2 dogs had a hemorrhagic lesion of the lung. Histopathologic examination revealed focal or diffuse interstitial pneumonitis, calcification of renal tubules, calcification of bronchial epithelial, renal tubular epithelial proliferation, myocardial fibrosis, fatty changes of the liver in several animals. Changes also found in control animals, but of lesser severity.	LOAEL: 660	Coon et al. 1970
Dog: 2	Inhalation	60	114 d, continuous	No significant effects.	NOAEL: 60	Coon et al. 1970
Pig: 8	Inhalation	50, 100, 150	4 wk	At 100 and 150 ppm, lethargy, nasal secretions, coughing, tracheal inflammation. Excessive lacrimation; reduced weight gain observed in all exposure groups.	LOAEL: 50	Drummond et al. 1980
Pig: 6	Inhalation	100	1-6 wk	Ocular irritation at wk 1, but not thereafter. No effects on appetite, mean daily weight gains, frequency of	LOAEL: 100	Doig and Willoughby 1971

				coughing, hemograms, total serum lactic dehydrogenase activity. Histopathologic changes included thickening of the tracheal epithelium, decrease in number of tracheal epithelial goblet cells in pigs exposed for 2-6 wk.		
Pig: 8	Inhalation	50, 100, 150	4 wk	Lethargy and an acute inflammatory reaction in the tracheal epithelium of pigs exposed at 100 or 150 ppm.	NOAEL: 50	Drummond et al. 1980
Pig: 9	Inhalation	10, 50, 100, 150	5 wk	Up to 50 ppm, coughing; irritation of the mouth, nose, eyes; reduced feed intake; and reduced weight gain. No effects observed at 10 ppm.	NOAEL: 10	Stombaugh et al. 1969
Pig: NS	Inhalation	100	31-45 d	Increased concentration of gamma globulin.	LOAEL: 100	Neumann et al. 1987 (as cited in ATSDR 1990)
Monkey: 3	Inhalation	220, 1,090	8 h/d, 5 d/wk for 6 wk	Histopathologic examination revealed focal pneumonitis in the lung of 1 of 3 animals at 220 ppm.	LOAEL: 220	Coon et al. 1970
Monkey: 3	Inhalation	660	90 d, continuous	Histopathologic examination revealed focal or diffuse interstitial pneumonitis, calcification of renal tubules, calcification of bronchial epithelial, renal tubular epithelial proliferation,	LOAEL: 660	Coon et al. 1970

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
				myocardial fibrosis, fatty changes of the liver in several animals. Changes were also found in control animals, but of lesser severity.		
Monkey: 3	Inhalation	60	114 d, continuous	No significant effects.	NOAEL: 60	Coon et al. 1970

Abbreviations: LC_{50}, median lethal concentration; LOAEL, lowest observable adverse effect level; NOAEL, no observable adverse effect level; NS, not specified.

vapor (or gas) will try to escape as quickly as possible (Swotinsky and Chase 1990). The odor threshold for ammonia is lower than is the threshold for irritation, and it can serve as a warning of ammonia's presence, but not as a determinant of its concentration. In the case of human deaths reported after massive inhalation exposures, laryngeal swelling resulting from fluid engorgement and edema restricted airflow (see Table 2–5). Further, in the first tissues exposed to the irritant gas, plasma exudes from the vascular walls into the respiratory passages causing additional blockage to airflow and leading to respiratory failure and death (Henderson and Haggard 1927). Hyperammonemia is an unlikely sequela from inhalation exposure to ammonia; however, the mechanism of hyperammonemia-induced CNS injury was discussed earlier.

Biomarkers of Exposure

There are no known specific biomarkers for exposure to ammonia. Plasma concentrations cannot serve this purpose, as relatively large amounts of ammonia are produced endogenously. Previously discussed studies (Schaerdel et al. 1983; Silverman et al. 1949) have demonstrated that inhalation of relatively high concentrations of ammonia do not significantly alter blood or urinary ammonia. Biomarkers of effect from ammonia exposure are limited to resultant tissue injuries from contact with the irritant gas. Unfortunately, the lesions are nonspecific and are consistent with exposure to other irritant gasses and caustic compounds.

Susceptible Populations

Persons who suffer from hepatic or renal insufficiency can become susceptible to ammonia toxicity. Toxicity from ammonia in these cases, however, results from endogenously produced ammonia. The limited systemic absorption of ammonia following inhalation exposure would be insignificant when compared with concentrations produced within the body (WHO 1986). Persons with hyperactive airway disease or other conditions that alter airway function (colds, cough, nasal congestion) are expected to be more susceptible to irritant effects of ammonia.

Adaptation

Adaptation to the odor and mild irritant effects of ammonia has been dem

onstrated in humans and appears to be a common occurrence in past occupational settings (Ferguson et al. 1977). Even more remarkable are the findings of Verberk (1977) who demonstrated that simple knowledge of the nature of the odor and the irritant effects of low concentrations of ammonia can significantly alter a subject's tolerance to the effects of the gas. The Navy should consider putting this later phenomenon to practice in training submarine crews for potential disabled submarine operations.

NAVY'S RECOMMENDED SEALS

The Navy proposes to set a SEAL 1 of 25 ppm for exposure to ammonia. This value is based on a report that some irritation can result from concentrations of 25 ppm (NIOSH 1974). The Navy has proposed a SEAL 2 of 75 ppm for ammonia. This value was based on reports of significant irritation at concentrations of 100 ppm (Vigliani and Zurlo 1955).

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Table 2–9 presents exposure limits for ammonia recommended by the NRC and other organizations. The 24-h emergency exposure guidance level (EEGL) is the most relevant guidance level to compare to the SEALs. EEGLs were developed for healthy military personnel for emergency situations. An important difference between the EEGLs and the SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for the EEGLs. Therefore, the SEAL values are higher than the corresponding EEGL values.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 25 ppm for ammonia is too conservative. The Navy's proposed SEAL 1 could be below the threshold for odor or perception for some crew members, and it is well below the concentrations shown consistently to cause minimal eye and throat irritation. The subcommittee recommends 75 ppm for SEAL 1. The

TABLE 2–9 Exposure Recommendations from Other Organizations

Organization	Type of Exposure Recommendation	Exposure Limit, ppm	Reference
EPA	RfC (lifetime)	0.14	IRIS 1991
ACGIH	TLV-TWA (8 h/d during 40-h workweek)	25	ACGIH 1999
	TLV-STEL (15 min)	35	
AIHA	ERPG1	25	AIHA 2001
	ERPG2	150	
	ERPG3	750	
ATSDR	MRL (≤14 d)	0.5	ATSDR 1990
	MRL (>14 d)	0.3	
DFG	MAK (8 h/d during 40 h workweek)	20	DFG 1997
	Peak Limit (5 min maximum duration, 8 times per shift)	40	
NASA[b]	SMAC (1 h)	30	NRC 1994
	SMAC (24 h)	20	
	SMAC (7 d)	10	
	SMAC (30 d)	10	
	SMAC (180 d)	10	
NIOSH	REL-TWA (10 h/d during 40-h workweek)	25	NIOSH 1992, 1997

Organization	Type of Exposure Recommendation	Exposure Limit, ppm	Reference
	REL-STEL (15 min)	35	
	IDLH	300	
NRC[a]	EEGL (1 h)	100	NRC 1987
	EEGL (24 h)	100	
	CEGL (90 d)	50	
OSHA	PEL-TWA (8 h/d during a 40-h workweek)	50	OSHA 1999[c]

[a]These guidelines were established for use by the military.
[b]These guidelines were established for use on spacecraft.
[c]Occupational Safety and Health Standards. Code of Federal Regulations. Part 1910.1000, Air Contaminants.
Abbreviations : ACGIH, American Conference of Governmental Industrial Hygienists; AIHA, American Industrial Hygiene Association; ATSDR, Agency for Toxic Substances and Disease Registry, CEGL, continuous exposure guidance level; DFG, Deutsche Forschungsgemeinschaft; EEGL, emergency exposure guidance level; EPA, U.S. Environmental Protection Agency, ERPG, emergency response planning guidelines; IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; MRL, minimal risk level; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; RfC, reference concentration; SMAC, spacecraft maximum allowable concentration; STEL, short-term exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

subcommittee's value is based on two controlled human studies. In one study, volunteers exposed to ammonia at concentrations above 100 ppm for 2–6 h/d, 5 d/wk for 6 wk experienced transient irritation of the eyes and throat but no decreased pulmonary function or impaired mental ability, no adverse effects were reported in volunteers exposed at 100 ppm or below (Ferguson et al. 1977). The other human study showed that exposure at 110 ppm for 2 h can cause irritation of the eyes and respiratory tract (Verberk 1977). Because adaptation to ammonia at low concentrations has been shown, minimal irritant effects that can occur from exposure below 75 ppm are not expected to worsen with a longer exposure (up to 10 d).

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 75 ppm for ammonia is too conservative. The subcommittee recommends a SEAL 2 of 125 ppm. This value is based on a controlled human study in which volunteers exposed to ammonia at 140 ppm experienced severe throat irritation and left the exposure chamber within 1.25 h, while volunteers exposed at 110 ppm reported eye and throat irritation but did not leave the exposure chamber for the duration of the experiment (2 h) (Verberk 1977). Ferguson et al. (1977) observed only transient irritation of the eyes and throat after extended exposures (2–6 h/d, 5 d/wk for 110 ppm), and there was no evidence that such exposure caused decreased pulmonary function or affected mental ability. The crew of a disabled submarine should be able to tolerate the irritant effects from exposure to ammonia at concentrations below 125 ppm for up to 24 h.

DATA GAPS AND RESEARCH NEEDS

Because most of the controlled human studies on ammonia are of relatively short durations (5–120 min), the subcommittee recommends that additional controlled studies of longer exposure durations (e.g., for at least 24 h, and if possible, for up to 10 d) be conducted.

There are data available on the interaction (altered toxicity) of ammonia with various chemicals, but there are little data available on the interaction of ammonia with other irritant gasses or airborne contaminants that are likely to be found in disabled submarines. Without evidence to the contrary, it might be assumed that the irritant effects of ammonia gas are at a minimum additive to the effects of other irritant gases that could be released simultaneously during a fire on a dis

abled submarine. However, the mechanism of irritation could be a saturable process, and the additive or synergistic nature of the effect might be an incorrect assumption. To address these questions, the subcommittee recommends that studies be conducted to examine the effects on respiratory-tract and eye irritation, and on pulmonary function of simultaneous exposures to multiple irritant gases.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Ammonia. Pp. 58–59 in Documentation of the Threshold Limit Values and Biological Exposure Indexes, Vol. 1., 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1999. TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents. Biological Exposure Indices. Cincinnati, OH: ACGIH.

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Alarie, Y. 1973. Sensory irritation by airborne chemicals. CRC Crit. Rev. Toxicol. 2(3): 299–363.

Alarie, Y. 1981. Bioassay for evaluating the potency of airborne sensory irritants and predicting acceptable levels of exposure in man. Food Cosmet. Toxicol. 19(5):623– 626.

Albrecht, J. 1996. Astrocytes and ammonia neurotoxicity. Pp. 137–153 in The Role of Glia in Neurotoxicity, M.Aschner and H.K.Kimelberg, eds. Boca Raton: CRC Press.

Anderson, D.P., C.W.Beard, and R.P.Hanson. 1964. The adverse effects of ammonia on chickens including resistence to infection with Newcastle disease virus. Avian Dis. 8:369–379.

Appelman, L.M., W.F.ten Berge, and P.G.J.Reuzel. 1982. Acute inhalation toxicity study of ammonia in rats with variable exposure periods. Am. Ind. Hyg. Assoc. J. 43(9):662–665.

ATSDR (Agency for Toxic Substancs and Disease Registry). 1990. Toxicological Profile for Ammonia. Prepared by Syracuse Research Corporation, for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. December.

Barrow, C.S., Y.Alarie, and M.F.Stock. 1978. Sensory irritation and incapacitation evoked by thermal decomposition products of polymers and comparisons with known sensory irritants. Arch. Environ. Health 33(2):79–88.

Boyd, E.M., M.L.MacLachlan, and W.F.Perry. 1944. Experimental ammonia gas poisoning in rabbits and cats. J. Ind. Hyg. Toxicol. 26(1):29–34.

Broderson, J.R., J.R.Lindsey, and J.E.Crawford. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. Am. J. Pathol. 85(1):115–130.

Buckley, L.A., X.Z.Jiang, R.A.James, K.T.Morgan, and C.S.Barrow. 1984. Respiratory tract lesions induced by sensory irritations at the RD50 concentration. Toxicol. Appl. Pharmacol. 74 (3):417–429.

Budavari, S., ed. 1989. Ammonia. Pp. 81 in The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Ed. Rahway, NJ: Merck.

Budavari S, M.J.O'Neil, A.Smith, P.E.Heckelman, and J.F.Kinneary. 1996. The Merck Index, 12th Ed. Rahway, NJ: Merck.

Burns, T.R., M.L.Mace, S.D.Greenberg, and J.A.Jachimczyk. 1985. Ultrastructure of acute ammonia toxicity in the human lung. Am. J. Forensic Med. Pathol. 6:204–210.

Caplin, M. 1941. Ammonia-gas poisoning. Forty-seven cases in a London shelter. Lancet 241(July 26):95–96.

Close, L.G., F.I.Catlin, and A.M.Cohn. 1980. Acute and chronic effects of ammonia burns on respiratory tract . Arch. Otolaryngol. 106(3):151–158.

Cole, T.J., J.E.Cotes, G.R.Johnson, H.de V.Martin, J.W.Reed, and M.J.Saunders. 1977. Ventilation, cardiac frequency and pattern of breathing during exercise in men exposed to *o*-chlorobenzylidene malonitrile (CS) and ammonia gas in low concentrations. Q. J. Exp. Physiol. Med. Sci. 62(4):341–351.

Coon, R.A., R.A.Jones, L.J.Jenkins, Jr., and J.Siegel. 1970. Animal inhalation studies of ammonia, ethylene glycol, formaldehyde, dimethylamine, and ethanol. Toxicol. Appl. Pharmacol. 16 (3):646–655.

Cooper, A.J.L., and F.Plum. 1987. Biochemistry and physiology of brain ammonia. Physiol. Rev. 67 (2):440–519.

Dalhamn, T. 1956. Mucus flow and ciliary activity in the trachea of healthy rats exposed to respiratory irritant gases (SO_2, NH_3, and HCHO). VIII. The reaction of the tracheal ciliary activity to single exposure to respiratory irritant gases and studies of the pH Acta Physiol. Scand. 36(Suppl. 123):93–105.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace. Report No. 33.1st Ed. Weinheim: Wiley-VCH.

Dodd, K.T., and D.R.Gross. 1980. Ammonia inhalation toxicity in cats: a study of acute and chronic respiratory dysfunction. Arch. Environ. Health 35(1):6–14.

Doig, P.A., and R.A.Willoughby 1971. Response of swine to atmospheric ammonia and organic dust. J. Am. Vet. Assoc. 159(11):1353–1361.

Drummond, J.G., S.E.Curtis, J.Simon, and H.W.Norton. 1980. Effects of aerial ammonia on growth and health of young pigs. J. Anim. Sci. 50(6):1085–1091.

Duda, G.D., and P.Handler. 1958. Kinetics of ammonia metabolism in vivo. J. Biol. Chem. 232:303–314.

Egle, J.L., Jr. 1973. Retention of inhaled acetone and ammonia in the dog. Am. Ind. Hyg. Assoc. J. 34(12):533–539.

el-Sewefy, A.Z., and S.Awad. 1971. Chronic bronchitis in an Egyptian ice factory. J. Egypt Med. Assoc. 54(5):304–310.

Erskine, R.J., P.J.Murphy, J.A.Langton, and G.Smith. 1993. Effect of age on the sensitivity of upper airway reflexes . Br. J.Anaesth. 70(5):574–575.

Ferguson, W.S., W.C.Koch, L.B.Webster, and J.R.Gould. 1977. Human physiological response and adaptation to ammonia. J. Occup. Med. 19(5):319–326.

Flury, F., and F.Zernick 1931. Noxious Gases, Vapors, Mist, Smoke and Dust Particles. Berlin: Springer.

Flury, K.E., D.E.Dines, J.R.Rodarte, and R.Rodgers. 1983. Airway obstruction due to inhalation of ammonia. Mayo Clin. Proc. 58(6):389–393.

Fürst, P., B.Josephson, G.Maschio, and E.Vinnars. 1969. Nitrogen balance after intravenous and oral administration of ammonium salts to man. J. Appl. Physiol. 26(1):13–22.

Gamble, M.R., and G.Clough. 1976. Ammonia build-up in animal boxes and its effect on rat tracheal epithlium. Lab. Anim. 10(2):93–104.

Gay, W.M.B., C.W.Crane, and W.D.Stone. 1969. The metabolism of ammonia in liver disease: a comparison of urinary data following oral and intravenous loading of [^{15}N] ammonium lactate. Clin. Sci. 37(3):815–823.

Guyton, A.C. 1981. Pp. 456–458, 889 in Textbook of Medical Physiology, 6th Ed. Philadelphia, PA: W.B.Sanders.

Hathaway, G.J., N.H.Proctor, J.P.Hughes, and M.L.Fischman. 1991. Pp. 83–84 in Proctor and Hughes' Chemical Hazards of the Workplace, 3rd Ed. New York Van Nostrand Reinhold.

Hatton, D.V., C.S.Leach, A.L.Beaudet, R.O.Dillman, and N.DiFerrante. 1979. Collagen breakdown and ammonia inhalation. Arch. Environ. Health 34(2):83–87.

Hawkins, R.A., and J.Jessy. 1991. Hyperammonemia does not impair brain function in the absence of net glutamine synthesis. Biochem. J. 277 (Pt.3):697–703.

Hawkins, R.A., J.Jessy, A.M.Mans, and M.R.De Joseph. 1993. Effect of reducing brain glutamine synthesis on metabolic symptoms of hepatic encephalopathy. J. Neurochem. 60(3):1000–1006.

Henderson, Y., and H.W.Haggard. 1927. Pp. 87, 113–126 in Noxious Gases and the Principles of Respiration Influencing Their Action. New York Chemical Catalog Company, Inc.

Henderson, Y., and H.W.Haggard. 1943. Characteristics of irritant gases. Pp. 125–126 in Noxious Gases, 2nd Ed. New York Reinhold.

Hilado, C.J., C.J.Casey, and A.Furst. 1977. Effect of ammonia on Swiss albino mice. J.Combust. Toxicol. 4:385–388.

Hoeffler, H.B., H.I.Schweppe, and S.D.Greenberg. 1982. Bronchiectasis following pulmonary ammonia burn. Arch. Pathol. Lab. Med. 106(13):686–687.

Holness, D.L., J.T.Purdham, and J.R.Nethercott. 1989. Acute and chronic respiratory effects of occupational exposure to ammonia. Am. Ind. Hyg. Assoc. 50(12):646– 650.

Industrial Bio-Test Laboratories, Inc. 1973. Irritation Threshold Evaluation Study with Ammonia, Industrial Bio-Test Laboratories, Inc. (Report to International Institute of Ammonia Refrigeration, Publication No. 663–03161).

IRIS. 1991. Ammonia. Integrated Risk Information System (IRIS), U.S. Environmental Protection Agency). [Online]. Available: http://www.epa.gov/iris [June 20, 2000].

Kapeghian, J.C., H.H.Mincer, A.B.Jones, A.J.Verlangieri, and I.W.Waters. 1982. Acute inhalation toxicity of ammonia in mice. Bull. Environm. Contam. Toxicol. 29(3):371–378.

Kass, I., N.Zamel, D.A.Dobry, and M.Holzer. 1972. Bronchiectasis following ammonia burns of the respiratory tract. A review of two cases. Chest 62(3):282–285.

Kirhov, V. 1977. Neuroautonomic responses of workers in the ammonia industry [in Bulgarian]. Suvrem. Med. 28(10):10–13.

Kustov, V.V. 1967. Means of determining the maximum allowable concentration of toxic products of natural human metabolism. Pp. 63–65 in General Questions of Industrial Toxicology, Moscow [in Russian]. NASA TT F-11,358.

Landahl, H.D., and R.G.Herrmann. 1950. Retention of vapors and gases in the human nose and lung. Arch. Ind. Hyg. Occup. Med. 1:36–45.

Leduc, D., P.Gris, P.Lheureux, P.A.Gevenois, P.De Vuyst, and J.C.Yernault. 1992. Acute and long term respiratory damage following inhalation of ammonia. Thorax 47(9):755–757.

Lehmann, K.B. 1886. Arch. F. Ind. Hyg. 5:68.

Levy, D.M., M.B.Divertie, T.J.Litzow, and J.W.Henderson. 1964. Ammonia burns of the face and respiratory tract. JAMA 190(10):95–98.

Lewis, R.J., ed. 1993. Hawle's Condensed Chemical Dictionary, 12th Ed. New York Van Nostrand Reinhold.

MacEwen, J.D., J.Theodore, and E.H.Vernot. 1970. Human exposure to EEL concentrations of monomethylhydrazine. Pp. 355–363 in Proceedings of the 1st Annual Conference on Environmental Toxicology, Ohio, Wright-Patterson Air Force Base, 9–11 September, 1970. AMRL-TR-70–102, Paper No. 23. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH.

MacEwen, J.D., and E.H.Vernot. 1972. Toxic Hazards Research Unit Annual Technical Report: 1972. AMRL-TR-72–62. NTIS AD755–358. Aerospace Medical Research Laboratory, Air Force Systems Command, Wright-Patterson Air Force Base, OH.

Mangold, C.A. 1971. Investigation of Occupational Exposure to Ammonia. Record of Industrial Hygiene Division Investigation, Puget Sound Naval Shipyard, Washington. 29 November 1971 .

Manninen, A., S.Anttila, and H.Savolainen. 1988. Rat metabolic adaptation to ammonia inhalation. Proc. Soc. Exp. Biol. Med. 187(3):278–281.

Markham, R.S. 1986. A Review of Damage from Ammonia Spills. Paper presented at the 1986 Ammonia Symposium, Safety in Ammonia Plants and Related Facilities. A.I.Ch.E., Boston, MA, August 1986. (Cited in Pedersen and Selig 1989).

Mayan, M.H., and C.P.Merilan. 1972. Effects of ammonia inhalation on respiration rate of rabbits. J. Anim. Sci. 34(3):448–452.

Mayan, M.H., and C.P.Merilan. 1976. Effects of ammonia inhalation on young cattle. N.Z. Vet. J. 24 (10):221–224.

Montague, T.J., and A.R.Macneil. 1980. Mass ammonia inhalation. Chest 77(4):496– 498.

Mulder, J.S., and H.O.Van der Zalm. 1967. A fatal case of ammonia poisoning. [In Dutch]. Tijdschrift voor Sociale Geneeskunde 45:458–460.

Neumann, R., G.Mehlhorn, I.Buchholz, U.Johannsen, and D.Schimmel. 1987. Experimental studies on the effect of chronic aerogenous toxic gas burden of suckling pigs with different ammonia concentrations. II. The reaction of cellular and humoral

infection defense mechanisms of NH3-exposed suckling pigs under the conditions of an experimental Pasteurella multocida infection with and without thermomotor stress [in German]. Zentralbl. Veterinarmed. [B] 34(4):241–253.

New Jersey Department of Health and Senior Services. 1998. Hazardous Substance Fact Sheet. Ammonia. New Jersey Dept. of Health and Senior Services, Trenton, NJ. June.

NIOSH (National Institute for Occupational Safety and Health). 1974. Criteria for a Recommended Standard Occupational Exposure to Ammonia. HEW74–136. U.S. Dept. of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1992. NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements. Pub. No. 92–100. U.S. Dept. of Health and Human Services, Cincinnati, OH. January.

NIOSH (National Institute for Occupational Safety and Health). 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Pub. No. 97–140. U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Washington, DC.

Norenberg, M.D. 1981. The astrocyte in liver disease. Pp. 303–352 in Advances in Cellular Neurobiology, Vol. 2., S.Fedoroff and L.Hertz, eds. New York: Academic Press.

Norenberg, M.D., and A.Martinez-Hernandez. 1979. Fine structural localization of glutamine synthetase in astrocytes of rat brain. Brain Res. 161(2):303–310.

NRC (National Research Council). 1979. Ammonia. Baltimore: University Park Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants. Vol. 7. Ammonia, Hydrogen Chloride, Lithium Bromide, and Toluene. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

O'Kane, G.J. 1983. Inhalation of ammonia vapour: a report on the management of eight patients during the acute stages. Anaesthesia 38(12):1208–1213.

OSHA (Occupational Safety and Health Administration). 1992. Occupational Safety and Health Guideline for Ammonia. Occupational Safety and Health Administration, U.S. Dept. of Labor. Division of Standards Development and Technology Transfer, NIOSH, U.S. Dept. of Health and Human Services.

Pedersen, F., and R.S.Selig. 1989. Predicting the consequences of short-term exposure to high concentrations of gaseous ammonia. J. Hazard. Mater. 21(2):143–159.

Pierce, J.O. 1994. Ammonia. Pp. 756–782 in Patty's Industrial Hygiene and Toxicology, 4th Ed., Vol. II, Part A. Toxicology, G.D.Clayton, and F.E.Clayton, eds. New York: John Wiley & Sohns.

Pitts, R.F. 1971. The role of ammonia production and excretion in regulation of acid-base balance. N. Engl. J. Med. 284(1):32–38.

Price, S.K., J.E.Hughes, S.C.Morrison, and P.D.Potgieter. 1983. Fatal ammonia inhalation: a case report with autopsy findings. S. Afr. Med. J. 64:952–955.

Prokop'eva, A.S., G.G.Yushkov, and I.O.Ubasheev. 1973. Data on the toxicologic characteristics of the single, brief effect of ammonia on animals [in Russian]. Gig. Tr. Prof. Zabol. 17(6):56–57.

Richards, P., C.L.Brown, B.J.Houghton, and O.M.Wrong. 1975. The incorporation of ammonia nitrogen into albumin in man: the effects of diet, uremia and growth hormone. Clin. Nephrol. 3(5):172–179.

Saul, R.L., and M.C.Archer. 1984. Oxidatipon of ammonia and hydroxylamine to nitrate in the rat and in vitro. Carcinogenesis 5(1):77–81.

Sax, N.I., and R.J.Lewis. 1987. Pp. 63–64 in Hawleys Condensed Chemical Dictionary, 11th Ed. New York: Van Nostrand Reinhold.

Schaerdel, A.D., W.J.White, C.M.Lang, B.H.Dvorchik, and K.Bohner. 1983. Localized and systemic effects of environmental ammonia in rats. Lab. Anim. Sci. 33(1):40–45.

Schoeb, T.R., M.K.Davidson, and J.R.Lindsey. 1982. Intracage ammonia promotes growth of *Mycoplasma pulmonis* in the respiratory tract of rats. Infect. Immun. 38(1):212–217.

Silver, S.D., and F.P.McGrath. 1948. A comparison of acute-toxicities of ethylene imine and ammonia to mice. J. Ind. Hyg. Toxicol. 30(1):7–9.

Silverman, L., J.L.Whiteenberger, and J.Muller. 1949. Physiological response of man to ammonia in low concentrations. J. Ind. Hyg. Toxicol. 31(2):74–78.

Slot, G.M. 1938. Ammonia gas burns. Lancet 2(Dec.):1356–1357.

Sobonya, R. 1977. Fatal anhydrous ammonia inhalation. Hum. Pathol. 8(3):293–299.

Stombaugh, D.P., H.S.Teague, and W.L.Roller. 1969. Effects of atmospheric ammonia on the pig. J. Anim. Sci. 28(6):844–847.

Stroud, S. 1981. Ammonia inhalation case report. Crit. Care Nurs. 1(2):23–26.

Swotinsky, R.B., and K.H.Chase. 1990. Health effects of exposure to ammonia: scant information. Am. J. Ind. Med. 17(4):515–521.

Takagaki, G., S.Berl, D.D.Clarke, D.P.Purpura, and H.Waelsch. 1961. Glutamic acid metabolism in brain and liver during infusion with ammonia labeled with nitrogen-15. Nature 189:326.

Targowski, S.P., W.Klucinski, S.Babiker, and B.J.Nonnecke. 1984. Effect of ammonia on in vivo and in vitro immune responses. Infect. Immun. 43(1):289–293.

Tepper, J.S., B.Weiss, and R.W.Wood. 1985. Alterations in behavior produced by inhaled ozone or ammonia. Fundam. Appl. Toxicol. 5(6 Pt 1):1110–1118.

Verberk, M.M. 1977. Effects of ammonia in volunteers. Int. Arch. Occup. Environ. Health 39(2):73–81.

Vigliani, E.C., and N.Zurlo. 1955. Experiences of the clinics Del Lavoro with some maximum concentrations of poisons of industry at the place of work [in German]. Arch. Gewerbepathol. Gewerbehyg. 13:528–534.

Visek, W.J. 1972. Effects of urea hydrolysis on cell life-span and metabolism. Fed. Proc. 31 (3):1178–93

Vitti, T.G., R.Vukmirovich, and O.H.Gaebler. 1964. Utilization of ammonia nitrogen, administered by intragastric, intraperitoneal, and subcutaneous routes: effects on growth hormone. Arch. Biochim. Biophys. 106:475–482.

Walton, M. 1973. Industrial ammonia gassing. Br. J. Ind. Med. 30(1):78–86.

Wands, R.C. 1981. Alkaline materials. Pp. 3045–3070 in Patty's Industrial Hygiene and Toxicology, Vol. 2B, Toxicology. G.D.Clayton, and F.E.Clayton, eds. 3rd Rev. Ed. New York: John Wiley and Sons.

Ward, K., B.Murray, and G.P.Costello. 1983. Acute and long-term pulmonary sequelae of acute ammonia inhalation. Irish Med. J. 76(6):279–281.

Warren, K.S., and S.Schenker. 1964. Effect of an inhibitor of glutamine synthesis (methionine sulfoximine) on ammonia toxicity and metabolism. J. Lab. Clin. Med. 64(3):442–449.

Weatherby, J.H. 1952. Chronic toxicity of ammonia fumes by inhalation. Proc. Soc. Exp. Biol. Med. 81:300–301.

Weedon, F.R., A.Hartzell, and C.Setterstrom. 1940. Toxicity of ammonia, chlorine, hydrogen cyanide, hydrogen sulfide, and sulfur dioxide gases. V. animals. Cont. Boyce Thompson Inst. 11:365–385.

White, E.S. 1971. A case of near fatal ammonia gas poisoning. J. Occup. Med. 13(11):549–550.

WHO (World Health Organization). 1986. Ammonia. Environmental Health Criteria 54. IPCS International Programme on Chemical Safety. Geneva: World Health Organization.

Zissu, D. 1995. Histopathological changes in respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15(3):207–213.

3

Carbon Monoxide

This chapter reviews physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on carbon monoxide. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine from exposure to carbon monoxide and to evaluate the Navy's proposed submarine escape action levels (SEALs), proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to carbon monoxide exposure.

BACKGROUND INFORMATION

Carbon monoxide is a colorless, odorless, tasteless gas (Budavari 1989). It is very flammable and burns in air with a bright blue flame. It is highly poisonous to humans. The chemical and physical properties of carbon monoxide are summarized in Table 3–1.

Trace quantities of carbon monoxide in the environment are considered normal (WHO 1999). Plants can both metabolize and produce this gas. Carbon monoxide is also produced by incomplete combustion of carbon-containing materials (ACGIH 1996), and automobile exhaust is a major source of carbon

monoxide in the environment (NRC 1994). Another common environmental source is cigarette smoke. Indoor sources include gas stoves, furnaces, and fires. Carbon monoxide is produced inside the body by hemoglobin metabolism (NRC 1994).

TABLE 3–1 Summary of Physical and Chemical Properties for Carbon Monoxide

Characteristic	Value
Formula	CO
CAS number	630–08–0
Molecular weight	28.01
Boiling point	–191.5°C
Melting point	–205°C
Vapor density	0.968
Conversion factors at 25°C, 1 atm	1 ppm=1.14 mg/m^3 1 mg/m^3=0.87 ppm

Abbreviations: atm, atmosphere; CAS, Chemical Abstract Service; mg/m^3, milligrams per cubic meter; ppm, parts per million.
Source: Budavari (1989); Lide (1991); NRC (1994).

TOXICOKINETIC CONSIDERATIONS

Carbon monoxide is absorbed through the lungs at an approximate rate of 25.8 ±8 mL/min-mm Hg (Jones et al. 1982). It is then absorbed into the bloodstream from the lungs. There is competitive binding between carbon monoxide and oxygen to hemoglobin in the red blood cell, forming carboxyhemoglobin (COHb) and oxyhemoglobin, respectively (WHO 1999). The rate of formation of COHb can be predicted by a model described by Coburn et al. (1965). The affinity of hemoglobin for carbon monoxide is approximately 200–250 times its affinity for oxygen (NRC 1985). The amount of COHb depends mainly on the concentration and duration of carbon monoxide exposure, and the barometric pressure. To a lesser extent, it is also dependent on minute volume, blood volume in lung capillaries, body temperature, rate of endogenous carbon monoxide production, average partial pressure of oxygen in the lung capillaries, and the exact ratio of the affinity of blood for carbon monoxide and oxygen. Figure 3–1 shows the relationship of carbon monoxide concentration in ambient air and the COHb concentration formed at various exposure times in human volunteers

(Spencer and Schaumburg 2000). Although the primary reaction of carbon monoxide is with hemoglobin, it also interacts with myoglobin, cytochromes, and metalloenzymes (e.g., cytochrome c oxidase and cytochrome P450) (WHO 1999). The health importance of these secondary reactions is not well understood.

COHb cannot carry oxygen, and the effect of binding is a reduction of tissue partial pressure of oxygen (pO_2) (NRC 1985). When carbon monoxide binds to hemoglobin, the affinity of the remaining hemoglobin for oxygen is increased. Therefore, the presence of COHb in the blood shifts the oxyhemoglobin dissociation curve to the left, and tissue pO_2 must decrease to much lower values for the oxyhemoglobin to release its oxygen. The combination of the decrease in oxygen-carrying capacity of the blood and the impaired release of oxygen to the tissues results in a greater tissue oxygen, deficiency than is produced by an equivalent reduction in ambient pO_2 (as at high altitude) or by an equivalent reduction in hemoglobin (as in anemia).

An additional hypothesis about the mechanism of carbon monoxide-mediated toxicity invokes reoxygenation injury subsequent to the hypoxic episode. Hyperoxygenation facilitates the production of reactive oxygen species, which, in turn, lead to the formation of oxidized proteins and nucleic acids (Zhang and Piantadosi 1992). Carbon monoxide exposure also has been shown to result in lipid peroxygenation (Thom 1990). Reoxygenation after exposure to carbon monoxide is also associated with oxidative stress and the ensuing production of oxygen radicals as a result of the conversion of xanthine dehydrogenase to xanthine oxidase (reperfusion injury; Thom 1992).

The lung eliminates carbon monoxide. More than 99% of this gas is eliminated unchanged, and less than 1% is converted to carbon dioxide (Stewart 1975). The time required for absorption or elimination of half the final volume of COHb in healthy, sedentary adults at sea level is 4 h (breathing air) or 1.5 h (breathing oxygen) (Stender et al. 1977).

HUMAN TOXICITY DATA

Carbon monoxide causes toxicity by binding reversibly to the hemoglobin molecule, forming COHb, which decreases the oxygen-carrying capacity of the blood. This capacity is further reduced because the presence of COHb alters the dissociation of oxyhemoglobin in the tissues.

Carbon monoxide toxicity has been studied well in humans. If sufficiently prolonged, exposure at concentrations of 200–1,200 ppm can result in a progression of such hypoxic symptoms as headache, decreased night vision, abnormal visual evoked response, nausea, abnormal fine manual dexterity, vomiting,

convulsions, and if no treatment is administered, death (NRC 1985). At 35% COHb, manual dexterity is impaired; at 40%, mental confusion is observed. Death can occur at 67% COHb. After treatment to increase pO_2, a complete recovery can be expected if tissue anoxia has not been too severe. The primary target organs of carbon monoxide are the heart and the brain, both of which have a critical need for oxygen (NRC 1994). The remainder of this section reviews the available human toxicity data on cardiovascular and central nervous system (CNS) effects after exposure to carbon monoxide; those data are summarized in Table 3–2.

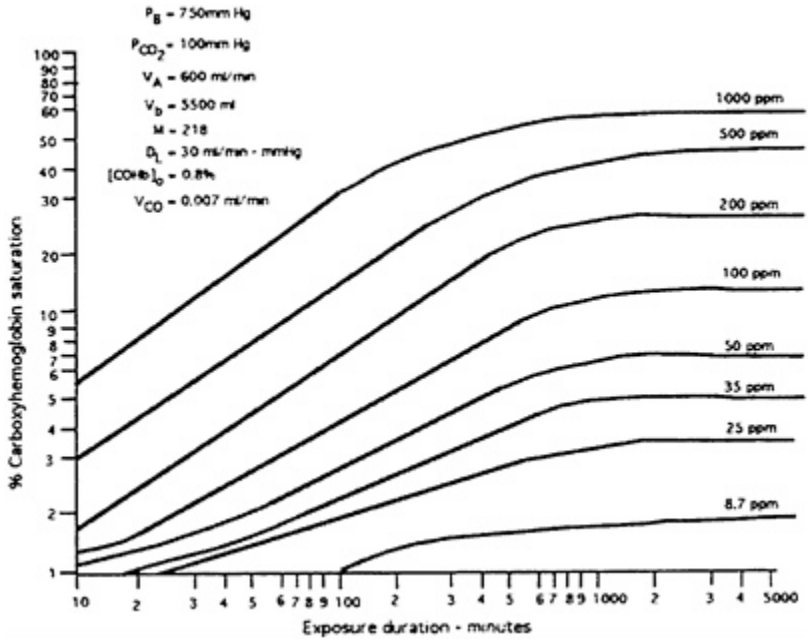

FIGURE 3–1 Carbon monoxide concentrations reached in blood (% saturation at various durations of exposure) in a normal human subject as a function of inspired CO. Abbreviations: P_B, barometric pressure; P_{CO2}, average partial pressure of carbon dioxide in lung capillaries; V_A, alveolar ventilation rate; V_b, blood volume; M, equilibrium constant; D_L, diffusing capacity of the lungs; $[COHb]_o$, control value prior to carbon monoxide exposure; V_{CO}, rate of endogenous carbon monoxide production. Source: Peterson and Stewart (1970). Reprinted with permission from Experimental and Clinical Neurotoxicology, 2nd Edition; copyright 2000, Oxford University Press.

TABLE 3-2 Human Toxicity Data, Inhalation Exposure to Carbon Monoxide

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
2	50	1 h and 20 min	Impaired vigilance. No effects on response latency, short-term memory, and ability to subtract numbers mentally.	Beard and Grandstaff 1975
2.3	26	2 h and 15 min	No effect on vigilance, heart rate, minute volume.	Horvath et al. 1971
2.3-3.1	50	80-125 min	Gradual decrease in vigilance performance.	Fodor and Winneke 1972
2.4	12	24 h/d, 8 d	3 of 16 subjects showed changes in P waves. 1 had marked S-T or T changes (subject had localized heart myopathy).	Davies and Smith 1980
2.5	50	25 min	Increased minute volume, reductions in duration (21-20 min) subjects could exercise maximally at 35°C.	Drinkwater et al. 1974
2.7	50	25 min	No effects on maximal oxygen uptake, minute volume, and heart rate.	Raven et al. 1974
3.4	NR	NR	Deficit in driving skills.	Wright et al. 1973
3-7.7	35, 76	4 h	No effect on visual task performance at 3%. Impairment of vigilance tasks at 4-7.7%.	Putz et al. 1976, 1979

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
4.3-5	50	4 h	During exercise, increase in heart rates, decrease in $VO_{2\,MAX}$, decreased time to exhaustion.	Horvath et al. 1975
4.5	NR	NR	Decrements in visual sensitivity.	McFarland et al. 1944, as cited in NRC 1985
5	100	2.5 h	No decrease in motor performance.	Mihevic et al. 1983
5-10	70	8 h/d, 13 yr	Holland Tunnel workers exposed for approximately 8 h/d for 13 yr. No adverse health effects observed.	Sievers et al. 1942
5.7	NR	NR	No decrement in vigilance.	Benignus et al. 1977; Davies et al. 1981
6.6	111	2 h and 15 min	Impaired vigilance. No effect on heart rate, minute volume.	Horvath et al. 1971
6.6	125	15 min-3 h	No effect on tracking performance, ability to estimate time lapse.	Mikulka et al. 1970
6.9	111	2 h and 15 min	No effect on vigilance, heart rate, minute volume.	O'Hanlon 1975
7.0	100	2.5 h	Impaired visual vigilance (no effect on auditory vigilance). Impaired performance in the Amthauer's Intelligence Structure Test.	Bender et al. 1972; Bunnell and Horvath 1989

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
7.1	50	24 h/d, 8 d	Feeling of fatigue. Increased minute volume, heart rate. Changes in P-waves.	Davies and Smith 1980; Davies et al. 1981
7.3 (non-smokers) – 9.3 (smokers)	NR	NR	No change in subjective symptoms, pulmonary function, oxygen metabolism, blood characteristics in healthy subjects performing moderate aerobic exercise at 50% of $VO_{2\,MAX}$	DeLucia et al. 1983, as cited in NRC 1985
7.5	250	15 min-1 h and 20 min	No effect on vigilance, response latency, short-term memory, ability to do subtraction. 23% reduction in the duration the subjects could exercise maximally.	Beard and Grandstaff 1975; Ekblom and Huot 1972
8-9	50-200	2.5-24 h	No effect on mental capacity, manual dexterity, hand steadiness, reaction time, estimation of time lapse, visual function.	Stewart et al. 1970; Ettema et al. 1975; Benignus et al. 1987; Luria and McKay 1979
8.5	650	45 min	Increased reaction time to visual stimuli.	Ramsey 1973
10	90	4-6 h	Increased response time, decreased precision in maintaining separation distance in driving.	Ray and Rockwell 1970

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
10.4	200	3 h	No effect on time perception, tracking performance.	O=Donnell et al. 1971
10.7-13.2	NR	NR	Minimal changes observed in heart rate, other physiologic responses in smokers and nonsmokers (aged 22-55) after long periods of activity.	Gliner et al. 1975, as cited in NRC 1985
11	75	24 h/d, 7 d	Changes in P-wave, S-T segment, or T-wave (6 of 9 subjects), supraventricular extrasystoles (1 of 9 subjects).	Davies and Smith 1980
11	700	NR	Gradual decrease in driving performance.	McFarland 1973
12	100	8 h	No effect on manual dexterity, hand steadiness, reaction time, estimation of time lapse.	Stewart et al. 1970
12	950	45 min	Increased reaction time. No effect on depth perception; light detection sensitivity.	Ramsey 1973
12.6	200	2 h and 40 min	No effect on vigilance performance.	Benignus et al. 1977
13-16	200-500	1-4 h	Mild headache.	Stewart et al. 1970
17	11,600 for 4-5 min, then 141.6 for remainder of experiment	2 h and 15 min	No effect on threshold to visually detect motion, pattern, contrast. No effect on luminance threshold.	Hudnell and Benignus 1989

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
18	200	5 h	No impairment on ability to estimate time lapse.	Stewart et al. 1973
15-20			No change in oxygen uptake in tissues during submaximal exercise for 5-60 min.	Chevalier et al. 1966; Ekblom and Huot 1972; Pirnay et al. 1971; Vogel and Gleser 1972; Vogel et al. 1972
20	100	NR	Headache in 1 of 49 subjects. No other symptoms. No changes in spinal and cranial nerve reflexes, heart rate, systolic and diastolic blood pressure, respiratory rate, muscle persistence time. No effect on static steadiness or response time in making simple choices of letter and color.	Schulte 1963
23	NR	NR	No changes in plasma volume, hematocrit, total protein concentration.	Parving 1972
37	860	NR	Severe headache, dizziness, difficulty in concentrating, polycythemia.	DiMarco 1988

COHb (%) a/v	Concentration, ppm	Exposure Duration	Effect	Reference
30-40	NR	NR	Severe headache, nausea and vomiting, syncope.	Stewart 1975, as cited in NRC 1985
40-45	NR	NR	Subjects unable to perform tasks requiring only slight physical exertion.	Chiodi et al. 1941, as cited in NRC 1985
50-60	NR	NR	Coma and convulsions.	Stewart 1975, as cited in NRC 1985
67-70	NR	NR	Lethal if not treated.	Stewart 1975, as cited in NRC 1985

Abbreviations: NR, not reported; VO_{2MAX}, maximum oxygen uptake.

Cardiovascular Effects

The myocardium is more sensitive than any other muscle tissue to the decrease in available blood oxygen caused by formation of COHb. Cardiac dysfunction attributable to the effects of carbon monoxide binding to cardiac myoglobin also could contribute to decreased perfusion of the heart and the CNS (Cobb and Etzel 1991). As COHb concentrations increase, there is a gradient of symptoms that reflects increasing cardiovascular dysfunction (Table 3–2). Some factors have been shown to modulate the clinical effects of carbon monoxide exposure. Greater oxygen demand in actively exercising (versus sleeping) patients enhances susceptibility to carbon monoxide intoxication (Meredith and Vale 1988). The degree and duration of hypotension, the presence of cardiac or pulmonary disease or anemia, as well as cardiac dysfunction (arrhythmias or other conditions) induced by carbon monoxide exposure also influence clinical outcome (Ehrich et al. 1944; Stewart 1976).

Cardiac function in healthy persons could be affected by low to moderate carbon monoxide exposures (Davies and Smith 1980). Six matched groups of young healthy subjects lived in a closed environmental chamber for 18 d and were exposed continuously to carbon monoxide at concentrations of 15 or 50 ppm in air during the middle 8 d. Unequivocal P-wave electrocardiogram (ECG) changes were observed during exposure in 3 of the 15 subjects exposed at 15 ppm (2.4% COHb) and in 6 of 15 subjects exposed at 50 ppm (7.1% COHb), compared with none of the 14 exposed at 0 ppm (0.5% COHb).

The ability to perform physical work is drastically reduced when COHb concentrations reach 40%. Chiodi et al. (1941) observed that subjects with 40– 45% COHb were unable to perform tasks requiring only slight physical exertion. COHb concentrations of 15–20% do not appear to affect the ability to do physical work (submaximal exercise for short durations) (Chevalier et al. 1966; Ekblom and Huot 1972; Pirnay et al. 1971; Vogel and Gleser 1972; Vogel et al. 1972). In those studies, a slight increase in heart rate was observed. Gliner et al. (1975) exposed smokers and nonsmokers aged 22–55 to carbon monoxide (13.2 and 10.7% COHb, respectively) during long periods of activity (3.5 h within a 4-h period) at 35% of maximal aerobic capacity. The subjects showed only minimal changes in physiologic response.

The critical concentration at which COHb reduces maximum oxygen uptake (VO_{2MAX}) is 4.3%, according to Horvath et al. (1975). The same investigators also reported decreases of 4.9% and 7% in work time to exhaustion at COHb of 3.3% and 4.3%, respectively. Those findings were confirmed in a double-blind study of 6 healthy male firefighters exposed to carbon monoxide (5.0–5.5% COHb for 4 h) (Klein et al. 1980). The firefighters showed a decrease in time to exhaustion.

Sievers et al. (1942) studied Holland Tunnel workers exposed for approximately 13 years at an average concentration of 70 ppm for multiple periods lasting 2 h each during an 8 h shift. No adverse health effects were observed in those workers. COHb concentrations were 5–10%. In a retrospective study of bridge and tunnel officers exposed to carbon monoxide at an average COHb concentration of less than 5%, Stern et al. (1988) reported a significant increase in mortality from arteriosclerotic heart disease. Given that continuous COHb burdens of 5% might carry a significant cardiovascular risk, it is possible that the cardiovascular effects of carbon monoxide in submariners, particularly those who smoke cigarettes, could be amplified by the imposition of a 1.5–5% COHb produced by ambient carbon monoxide in a submarine (Bondi et al. 1978; Davies 1973; Goldsmith and Landaw 1968; McIlvaine et al. 1969).

Central Nervous System Effects

Numerous studies have assessed the effects of carbon monoxide on such CNS functions as vigilance, sensory effects, coordination and tracking, driving ability, and cognitive behavior. Despite extensive investigations, the COHb concentrations that trigger an effect on human perceptual function and cognition have not been quantified. COHb concentrations as low as 4.5% perturb ability to discriminate small differences in light intensity (McFarland et al. 1944). Transient alterations of visual thresholds are associated with 5% COHb (McFarland et al. 1944). A significant performance decrement in the ability to compare the duration of tones was reported after exposure to 50 and 100 ppm carbon monoxide for 90 and 50 min, respectively (Beard and Grandstaff 1975). Other studies have not corroborated effects on perceptual function and cognition at comparably low COHb concentrations (Table 3–2). Differences in experimental design-in particular, in task duration–have been suggested to be, at least partially responsible for the discrepant results (Beard and Grandstaff 1975; Crystal and Ginsberg 2000; Stewart 1976).

Vigilance assessment measures how well a person performs at detecting small environmental changes that take place at unpredictable intervals and, therefore, demand continuous attention (NRC 1985). Decreases in vigilance due to carbon monoxide exposure have been reported by several investigators, but the data do not show conclusively which concentration of COHb will trigger impaired vigilance. Beard and Grandstaff (1975) reported impaired vigilance in subjects with 2% COHb. Horvath et al. (1971) and O'Donnell et al. (1971) reported a decrement in performance in subjects with 6.6% COHb. However, vigilance was not affected in subjects with 0.9% and 2.3% COHb. Winneke et al. (1978) did not observe any decrements in vigilance at COHb up to 11%. Putz et al. (1976, 1979) exposed subjects to carbon monoxide and found that visual-task performance was decreased at 5% COHb. This effect was not observed at 1% or 3% COHb. Using a vigilance paradigm different from that used by Putz et al. (1976, 1979), Benignus et al. (1977) and Davies et al. (1981) found no decrement in vigilance in subjects with up to 5.7% COHb.

Several studies have tested visual function after exposure to carbon monoxide. To minimize variability, McFarland et al. (1944) studied brightness discrimination in a small group of well-trained subjects. The subjects reported decreases in visual sensitivity at approximately 4.5% COHb. Another study reported no adverse effects on visual discrimination or depth perception in subjects with 8% or 12% COHb (Ramsey 1973). Luria and McKay (1979) reported no decrement in night vision with COHb of 9%. Davies et al. (1981) reported that at 7% COHb there was no effect on visual function. The studies described above used various visual paradigms, which could account for the differences in results.

Two studies that used subjects with COHb concentrations of up to 15% reported no changes in the ability to do tasks involving coordination (Stewart et al. 1970; Wright et al. 1973). Stewart et al. (1970) used several tests of manual dexterity. In one, subjects had to pick up small pins, place them in small holes, and then put collars over the pins. No effects attributable to carbon monoxide exposure were found at COHb up to 15%. Wright et al. (1973) also observed no effects on a number of coordination tasks at COHb of 5% and 7%. One study did report a decrement in a hand-eye coordination task (5% COHb) (Putz et al. 1976).

Several investigators have assessed the effects of carbon monoxide exposure on driving performance. McFarland (1973) studied subjects with 17% COHb who drove instrumented automobiles under highway conditions. Carbon monoxide did not cause a serious decrease in driving ability, but there was a statistically significant increase in roadway viewing time. No differences were reported in steering-wheel reversals. At 10% COHb and higher, Ray and Rockwell (1970) reported a significant difference in time required to respond to a velocity change in a lead car.

Bender et al. (1972) investigated the effects of exposure that resulted in 7% COHb on the ability to learn 10 nonsense syllables. The exposure caused a decrease in ability to recite the syllables and a decrease in ability to recite a series of digits in reverse order. The exposed subjects showed no change in ability to perform other tasks involving calculation problems, analogies, shape selection, dot counting, and letter recognition.

In approximately 3% of patients recovering from acute carbon-monoxide-induced coma, a severe, sometimes fatal, neurologic condition develops (Choi 1983; Min 1986). No clinical or laboratory results predict which patients are at risk for the delayed neuropsychiatric syndrome. Age appears to be a risk factor (Ernst and Zibrak 1998). Although the syndrome is widely held as a characteristic of carbon monoxide poisoning, a similar illness also can develop upon hypoglycemia, heroin overdose, strangulation, and anesthetic accident (Plum et al. 1962). The delayed syndrome is characterized as a postanoxic encephalopathy syndrome. It commonly develops 1–4 wk after an acute episode, with carbon-monoxide-induced coma and a period of recovery and lucid state. Thereafter, irritability, confusion, or manic symptoms appear, followed by a spastic or parkinsonian gait. Masked faces and rigidity are common, and most patients become somnolent and unable to walk On occasion, patients become mute or comatose, and some die. Notably, the progress of the disease can be halted at any stage, and some patients can make partial or full recovery. The most striking change associated with the delayed syndrome is diffuse demyelination in the cerebral hemispheres. Unlike injury patterns that occur in the acute carbon mon

oxide syndrome, the corpus callosum, fornix, and anterior commissure are commonly spared.

EXPERIMENTAL ANIMAL TOXICITY DATA

Numerous studies have been conducted to test carbon monoxide toxicity in experimental animals. Several are reviewed in this section and summarized in Table 3–3.

Acute Exposure

There is evidence that acute exposure (20 min to 6 h) to carbon monoxide causes cardiovascular and CNS effects in experimental animals. Dogs exposed at 100 ppm (6.5% COHb) for 2 h (Aronow et al. 1979) and monkeys exposed at 100 ppm (9.3% COHb) for 6 hours showed a decrease in ventricular fibrillation threshold (DeBias et al. 1976). No effects on unconditioned reflex and conditioned avoidance tests were observed in rats exposed to 400 ppm (27% COHb) for 4 h (Mullin and Krivanek 1982). Failure of unconditioned reflex and a decrement in conditioned avoidance were observed in rats exposed to 800 ppm (34% COHb) for 4 h (Mullin and Krivanek 1982), and increased time to traverse a maze was observed in rats exposed to 2,000 ppm (75% COHb) for 30 min (Annau 1987). Monkeys exposed to 900 ppm (25–30% COHb) for 20–30 min showed a decrement in the ability to perform behavioral tasks (Purser and Berrill 1983). After 10–15 min exposure, the monkeys also had a decrease in carbon dioxide output.

Repeated Exposure

Repeated (subchronic and chronic) exposure of experimental animals to carbon monoxide increases hemoglobin concentration and hematocrit in several animal species. These effects were observed in exposures at 50 ppm for 6 mo (7.3% COHb) in dogs (Musselman et al. 1959), at 96 ppm for 90 d (7.5% COHb) in rats (Jones et al. 1971), and at 200 ppm for 90 d (16–20% COHb) in rats and monkeys (Jones et al. 1971). The effects were not observed at lower COHb concentrations, for example, in exposures at 20 ppm for 2 yr (3.4% COHb) in monkeys (Eckardt et al. 1972), at 51 ppm for 90 d (5% COHb) in monkeys and rats (Jones et al. 1971), and at 66 ppm for 2 yr (7.4% COHb) in monkeys (Eckardt et al. 1972).

TABLE 3-3 Experimental Animal Toxicity Data, Exposure with Carbon Monoxide

Species	Concentration, ppm	Duration	COHb (%)	Effect	Reference
ACUTE EXPOSURE					
Dog	100	2 h	6.5	Decreased ventricular fibrillation threshold.	Aronow et al. 1979
Monkey	100	6 h	9.3%	Decreased ventricular fibrillation threshold.	DeBias et al. 1976
Rat	400	4 h	27	No effect on unconditioned reflex, conditioned avoidance tests.	Mullin and Krivanek 1982
Monkey	900	20-30 min	25-30	Effect on ability to perform behavioral tasks. Metabolism affected (decreased CO_2 output) after 10-15 min exposure.	Purser and Berrill 1983
Rat	800	4 h	34	Failure of unconditional reflex, decrement in conditioned avoidance.	Mullin and Krivanek 1982
Rat	2000	30 min	75	Increased time to traverse a maze.	Annau 1987
REPEATED EXPOSURE					
Monkey	20	22 h/d, 7 d/wk, 2 yr	3.4	No change in hematocrit, hemoglobin concentration, red blood cell count. No histopathology in heart, brain, lung.	Eckardt et al. 1972
Monkey, Rat	51	24 h/d, 90 d	5 at 48 h	No toxic signs and histopathology. No changes in hematocrit, hemoglobin concentration.	Jones et al. 1971

Species	Concentration, ppm	Duration	COHb (%)	Effect	Reference
Dog	50	24 h/d, 6 mo	7.3	12% increase in hemoglobin concentration. No change on EKG, histology.	Musselman et al. 1959
Monkey	66	22 h/d, 7 d/wk, 2 yr	7.4	No change in hematocrit, hemoglobin concentration, red blood cell count. No histopathology in heart, brain, lung.	Eckardt etal. 1972
Rat	96	24 h/d, 90 d	7.5 at 48 h	No toxic signs and histopathology. Increased hematocrit and hemoglobin concentrations.	Jones et al. 1971
Monkey	96	24 h/d, 90 d	10 at 48 h	No toxic signs, histopathology. No effects on hematocrit, hemoglobin concentrations.	Jones et al. 1971
Monkey Rat	200	24 h/d, 90 d	16-20	No toxic signs, histopathology. Increased hematocrit, hemoglobin concentrations.	Jones et al. 1971
Monkey	400	0.5 h on/0.5 h off, 10 h/d for 12 mo	18-23	Did not cause atherosclerosis.	Bing et al. 1980
Dog	100	5 3/4 h/d, 6 d/wk for 11 wk	20	Increases in red blood cell count after 8 wk; returned to normal after 11 wk.	Brieger 1944
Dog	100	5 3/4 h/d, 6 d/wk for 11 wk	20	T-wave changes, myocardial degeneration.	Ehrich et al. 1944

Dog	100	5 3/4 h/d, 6 d/wk for 11 wk	20	Disturbance of postural and position reflexes and of gait. Histologic changes in cortex, white matter of the cerebral hemispheres, globus pallibus, brain stem 3 mo after exposure.	Lewey and Drabkin 1944
Monkey	380	24 h/d, 99 d	31	No decrement on operant behavior: visual and auditory response times, learned pressing of a lever.	Theodore et al. 1971
Monkey, Dog, Rat, Mouse	400 for 71 d, then 500 for 97 d	24 h/d, 71 and 97 d	32-33	40% increase in hemaglobin concentration, 30% increases in hematocrit, blood volume. No effect on plasma volume, body weight, survival. No histopathology in brain, heart. In rats, heart and spleen increased in weight.	Theodore et al. 1971
Rat	500	21 h/d, 62 d	42	Enhanced development of NaCl-induced hypertension, cardiomegaly, splenomegaly, elevated hemoglobin concentration, hematocrit.	Shiotsuka et al. 1984
Rat	25 50	24 h/d, 2 mo	NR	At 25 ppm, no effects on serum corticosterone and thyroxine, hypothalamic norepinephrine concentration, adrenal catecholamines concentration, organ weights, body weight. At 50 ppm, reduced serum thyroxine concentration, increased adrenal catecholamine concentration. No effect on organ weight.	Vyskocil et al. 1986

Species	Concentration, ppm	Duration	COHb (%)	Effect	Reference
	100			At 100 ppm, reductions in serum thyroxine and hypothalmic norepinephrine concentrations, increases in adrenal catecholamines and serum cortocosterone, no effect on body organ weight except for a slight decrease in liver weight.	

Abbreviation: NR, not reported.

Several studies have examined the morphologic effects of carbon monoxide exposure in experimental animals. Dogs exposed at 100 ppm for 5.75 h/d, 6 d/wk for 11 wk (20% COHb) exhibited histopathologic changes in the cortex, white matter of the cerebral hemispheres, globus pallidus, and brain stem 3 mo after exposure (Lewey and Drabkin 1944). These animals also showed disturbance of postural and position reflexes and of gait. No histopathologic changes were observed in exposures at 50 ppm for 6 mo (7.3% COHb) in dogs (Musselman et al. 1959), at 200 ppm for 90 d (16% COHb) in rats (Jones et at. 1971), at 66 ppm for 2 yr (7.4% COHb) in monkeys (Eckardt et al. 1972), at 200 ppm for 90 d (20% COHb) in monkeys (Jones et al. 1971), and at 400 ppm for 71 d (32% COHb) followed by 500 ppm for 97 d (33% COHb) in monkeys, dogs, rats, and mice (Theodore et al. 1971).

NAVY'S RECOMMENDED SEALS

The Navy has proposed a SEAL 1 set at 75 ppm and a SEAL 2 set at 85 ppm. These values are based on a model developed by Coburn et al. (1965) for estimating COHb concentrations from environmental exposures. COHb at these values would range from 8.3% to 12.4%.

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Recommended exposure guidance levels for carbon monoxide from the NRC and other organizations are summarized in Table 3–4. The 24-h emergency exposure guidance level (EEGLs) (NRC 1985) is the most relevant guidance level to compare to the SEALs. EEGLs were developed for healthy military personnel in emergency situations. An important difference between EEGLs and SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. Therefore, the SEAL values are higher than the corresponding EEGL values.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 75 ppm for carbon monoxide is too conservative. The subcommittee rec

TABLE 3–4 Recommendations from Other Organizations for Carbon Monoxide

Organization	Type of Exposure Level	Recommended Exposure Level	Reference
ACGIH	TLV-TWA	25 ppm	ACGIH 1998
AIHA	ERPG-1	200 ppm	AIHA 2001
	ERPG-2	350 ppm	
	ERPG-3	500 ppm	
DFG	MAK (8 h/d, 40 h/wk)	30 ppm	DFG 1997
	Peak Limit (30 min maximum duration, 4 times per 8 h)	60 ppm	
IPCS	Derived guidelines values for carbon monoxide concentration in ambient air		WHO 1999
	15 min	87 ppm	
	30 min	52 ppm	
	1 h	26 ppm	
	8 h	9 ppm	
NAC	Proposed 8-h AEGL-1	NR	Federal Register: May 2, 2001.66(85):21940–21964.
	Proposed 8-h AEGL-2	27	
	Proposed 8-h AEGL-3	130	
NASA	SMAC:		NRC 1994
	1 h	55 ppm	
	24 h	20 ppm	
	7d	10 ppm	
	30 d	10 ppm	
	180 d	10 ppm	
NIOSH	REL	35 ppm (Time Weighted Average)	

		200 ppm (Ceiling Concentration)	
NIOSH	IDLH	1,200 ppm	NIOSH 2000
NRC	EEGL:		NRC 1985
	10 min	1,500 ppm	
	30 min	750 ppm	
	60 min	400 ppm	
	24 h	50 ppm	

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AIHA, American Industrial Hygiene Association; DFG, Deutsche Forschungsgemeinschaft; IPCS, International Programme on Chemical Safety; NAC, National Advisory Committee; NASA, National Aeronautics and Space Administration; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; WHO, World Health Organization; AEGL, acute exposure guideline level; EEGL, emergency exposure guidance level; ERPG, emergency response planning guidelines; IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; NR, not recommended; PEL, permissible exposure limit; REL, recommended exposure limit; SMAC, spacecraft maximum allowable concentration; TLV-TWA, Threshold Limit Value—time weighted average.

ommends a SEAL 1 of 125 ppm; exposure at this concentration would not result in blood COHb concentration above 15%. Studies in humans show that COHb concentrations of approximately 15% do not result in significant effects on perceptual function or cognition in healthy individuals (Stewart et al. 1973; Hudnell and Benignus 1989).

It should be noted that the SEAL 1 was recommended within the context of inspired air at sea level, where the oxygen concentration is at 20.95%. The oxygen concentration in a disabled submarine may be lower. Oxygen and carbon monoxide compete for binding sites on hemoglobin. When the oxygen pressure is low in the lung capillaries, as might be found in crew members on a disabled submarine, there is more unoxygenated hemoglobin for carbon monoxide to bind to. Therefore, carbon monoxide exposure becomes more dangerous to crew members in a submarine with lower oxygen concentration than one in which the oxygen concentration is 20.95%. The partial pressure of carbon monoxide (Pco) should be proportional to the partial pressure of alveolar oxygen (PAo_2). Therefore, in a disabled submarine with 16% oxygen concentration instead of 20.95%, the inspired Po_2 would be 114 mm Hg, PAo_2=64 mm Hg (PAo_2=(P_B-47)-50 mm Hg; where P_B is barometric pressure). Because Pco/Po_2 =1/220×Po_2, in equilibrium the ratio would reduce the allowable carbon monoxide from the proposed 125 ppm carbon monoxide to 80 ppm (64/100×125).

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 85 ppm for carbon monoxide is too conservative. The subcommittee recommends a SEAL 2 of 150 ppm, which would not result in blood COHb concentration above 20%. Human data suggest that at a COHb concentration of approximately 20%, some submariners could experience mild headache and some decrement in cognitive function (Schulte 1963; Parving 1972; Stewart et al. 1973). Such effects would not impair the ability of a crew to escape from a disabled submarine. The recommended SEAL 2 is also supported by Theodore et al. (1971) where monkeys were exposed to a carbon monoxide concentration of 380 ppm for 90 d (COHb=31%) and there were no adverse health effects.

As pointed out in the discussion on SEAL 1, the recommended value for SEAL 2 is set for oxygen concentration at sea level (20.95%). Given that the oxygen concentration in the disabled submarine will likely be lower, it is necessary to correct the SEAL 2 for this change. Applying the same assumptions and calculations, one derives a SEAL 2 of 96 ppm (64/100×150) for a submarine in which the oxygen concentration is at 16%.

DATA GAPS AND RESEARCH NEEDS

The subcommittee recommends that the Navy consider conducting the following studies:

- Studies to determine whether the rates of formation and elimination of COHb will increase under hyperbaric conditions. Such studies should be conducted because carbon monoxide exerts its toxic effects by reduction of the oxygen-carrying capacity of the blood. Thus, the ratio of the pressure of carbon monoxide and the pressure of oxygen will determine the toxicity of carbon monoxide. This ratio will not be affected by absolute pressure.
- Studies on the additive effects of carbon monoxide and hydrogen cyanide, at concentrations likely to be produced in disabled submarines.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1996. Carbon Monoxide. Pp. 1–4. Supplements to the 6th Edition Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH: ACGIH

ACGIH (American Conference of Governmental Industrial Hygienists). 1998. Pp. 81– 83 in TLVs and BEIs Threshold Limit Values for Chemical Substances and Physical Agents. Cincinnati, OH: ACGIH

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Annau, Z. 1987. Complex maze performance during carbon monoxide exposure in rats. Neurotoxicol. Teratol. 9(2):151–155.

Aronow, W.S., E.A.Stemmer, and S.Zweig. 1979. Carbon monoxide and ventricular fibrillation threshold in normal dogs. Arch. Environ. Health 34(3):184–186.

Beard, R.R., and N.W.Grandstaff. 1975. Carbon monoxide and human functions. Pp. 1–27 in Environmental Science Research, Vol. 5. Behavioral Toxicology, B.Weiss and V.G.Laties, eds. New York: Plenum Press.

Bender, W., M.Goethert, and G.Malorny. 1972. Effect of low carbon monoxide concentrations on psychological functions. Staub-Reinhalt Luft. 32(4):54–60.

Benignus, V.A., K.E.Muller, C.N.Barton, and J.D.Prah. 1987. Effect of low level carbon monoxide on compensatory tracking and event monitoring. Neurotoxicol. Teratol. 9(3):227–234.

Benignus, V.A., D.A.Otto, J.D.Prah, and G.Benignus. 1977. Lack of effects of carbon monoxide on human vigilance. Percept. Mot. Skills 45(3 Pt 1):1007–1014.

Bing, R.J., J.S.Sarma, R.Weishaar, A.Rackl, and G.Pawlik. 1980. Biochemical and histological effects of intermittent carbon monoxide exposure in cynomolgus monkeys (Macaca fascicularis) in relation to atherosclerosis. J. Clin. Pharmacol. 20(8– 9):487–499.

Bondi, K.R., K.R.Very, and K.E.Schaefer. 1978. Carboxyhemoglobin levels during a submarine patrol. Aviat. Space Environ. Med. 49(7):851–854.

Brieger, H. 1944. Carbon monoxide polycythemia. J. Ind. Hyg. Toxicol. 26(10):321–327.

Budavari, S., ed. 1989. Carbon monoxide. Pp. 275 in The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Ed. Rahway, NJ: Merck.

Bunnell, D.E., and S.M.Horvath. 1989. Interactive effects of heat, physical work and CO exposure on metabolism and cognitive task performance. Aviat. Space Environ. Med. 60(5):428–432.

Chevalier, R.B., R.A.Krumholz, and J.C.Ross. 1966. Reaction of nonsmokers to carbon monoxide inhalation: cardiopulmonary responses at rest and during exercise. JAMA 198(10):1061–1064.

Chiodi, H., D.B.Dill, F.Consolazio, and S.M.Horvath. 1941. Respiratory and circulatory responses to acute carbon monoxide poisoning. Am. J. Physiol. 134:683–693.

Choi, I.S. 1983. Delayed neurologic sequelae in carbon monoxide intoxication. Arch. Neurol. 40 (7):433–435.

Cobb, N., and R.A.Etzel. 1991. Unintentional carbon monoxide-related deaths in the United States, 1979 through 1988. JAMA 266(5):659–663.

Coburn, R.F., R.E.Forster, and P.B.Kane. 1965. Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. J. Clin. Invest. 44 (11):1899–1910.

Crystal, H.A., and M.D.Ginsberg. 2000. Carbon Monoxide. Pp. 318–329 in Experimental and Clinical Neurotoxicology, Second Ed., P.S.Spencer, H.H.Schaumburg, and A.C.Ludolph, eds. New York, NY: Oxford University Press.

Davies, D.M. 1973. Sixty days in a submarine: the pathophysiological and metabolic cost. J.R.Coll. Physicians Lond. 7(2):132–144.

Davies, D.M., and D.J.Smith. 1980. Electrocardiographic changes in healthy men during continuous low-level carbon monoxide exposure. Environ. Res. 21(1):197– 206.

Davies, D.M., E.J.Jolly, R.J.Pethybridge, and W.P.Colquhoun. 1981. The effects of continuous exposure to carbon monoxide on auditory vigilance in man. Int. Arch. Occup. Environ. Health 48(1):25–34.

DeBias, D.A., C.M.Banerjee, N.C.Birkhead, C.H.Green, S.D.Scott, and W.V.Harrer. 1976. Effects of carbon monoxide inhalation on ventricular fibrillation. Arch. Environ. Health 31(1):42–46.

DeLucia, A.J., J.H.Whitaker, and L.R.Bryant. 1983. Effects of combined exposure to ozone and carbon monoxide (CO) in humans. Pp. 145–159 in Advances in Modern Environmental Toxicology, Vol. 5, S.D.Lee, M.G.Mustafa, and M.A.Mehlman, eds. Princeton, NJ: Princeton.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, 1st Ed. Report No. 33. Weinheim: Wiley-VCH.

DiMarco, A. 1988. Carbon monoxide poisoning presenting as polycythemia. N. Engl. J. Med. 319 (13):874.

Drinkwater, B.L., P.B.Raven, S.M.Horvath, J.A.Gliner, R.O.Ruhling, N.W.Bolduan, and S.Tagucki. 1974. Air pollution, exercise, and heat stress. Arch. Environ. Health 28(4):177–181.

Eckardt, R.E., N.H.McFarland, Y.C.Alarie, and W.M.Busey. 1972. The biologic effect from long-term exposure of primates to carbon monoxide. Arch. Environ. Health 25(6):381–387.

Ehrich, W.E., S.Bellet, and F.H.Lewey. 1944. Cardiac changes from CO poisoning. Am. J. Med. Sci. 208:511–523.

Ekblom, B., and R.Huot. 1972. Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta. Physiol. Scand. 86(4):474–482.

Ernst, A., and J.D.Zibrak. 1998. Carbon monoxide poisoning. N. Engl. J. Med. 339(22):1603–1608.

Ettema, J.H., R.L.Zielhuis, E.Burer, H.A.Meier, L.Kleerekoper, and M.A.de Graaf. 1975. Effects of alcohol, carbon monoxide and trichloroethylene exposure on mental capacity. Int. Arch. Occup. Environ. Health 35(2):117–132.

Fodor, C.G., and G.Winneke. 1972. Effect of low CO concentrations on resistance to monotony and on psychomotor capacity. Staub-Reinhalt Luft 32(4):46–54.

Gliner, J.A., P.B.Raven, S.M.Horvath, B.L.Drinkwater, and J.C.Sutton. 1975. Man's physiologic response to long-term work during thermal and pollutant stress. J. Appl. Physiol. 39 (4):628–632.

Goldsmith, J.R., and S.A.Landaw. 1968. Carbon monoxide and human health. Science 162 (860):1352–1359.

Horvath, S.M., T.E.Dahms, and J.F.O=Hanlon. 1971. Carbon monoxide and human vigilance: a deleterious effect of present urban concentrations. Arch. Environ. Health 23(5):343–347.

Horvath, S.M., P.B.Raven, T.E.Dahms, and D.J.Gray. 1975. Maximal aerobic capacity at different levels of carboxyhemoglobin. J. Appl. Physiol. 38(2):300–303.

Hudnell, H.K., and V.A.Benignus. 1989. Carbon monoxide exposure and human visual detection thresholds. Neurotoxicol. Teratol. 11(4):363–371.

Jones, R.A., J.A.Strickland, J.A.Stunkard, and J.Siegel. 1971. Effects on experimental animals of long-term inhalation exposure to carbon monoxide. Toxicol. Appl. Pharmacol. 19(1):46–53.

Jones, H.A., J.C.Clark, E.E.Davies, R.E.Forster, and J.M.Hughes. 1982. Rate of uptake of carbon monoxide at different inspired concentrations in humans. J. Appl. Physiol. 52(1):109–113.

Klein, J.P., H.V.Foster, R.D.Stewart, and A.Wu. 1980. Hemoglobin affinity for oxygen during short-term exhaustive exercise. J. Appl. Physiol. 48(2):236–242.

Lewey, F.H., and D.L.Drabkin. 1944. Experimental chronic carbon monoxide poisoning of dogs. Am. J. Med. Sci. 208:502–511.

Lide, D.R. 1991. CRC Handbook of Chemistry and Physics, 72nd Ed. Boca Raton: CRC Press.

Luria, S.M., and C.L.McKay. 1979. Effects of low levels of carbon monoxide on visions of smokers and nonsmokers. Arch. Environ. Health 34(1):38–44.

McFarland, R. 1973. Low-level exposure to carbon monoxide and driving performance. Arch. Environ. Health 27(6):355–359.

McFarland, R.A., F.J.W.Roughton, M.H.Halperin, and J.I.Niven. 1944. The effects of carbon monoxide and altitude on visual thresholds. J. Aviat. Med. 15:381–394.

McIlvaine, P.M., W.C.Nelson, and D.Bartlett Jr. 1969. Temporal variation of carboxyhemoglobin concentrations. Arch. Environ. Health 19(1):83–91.

Meredith, T., and A.Vale. 1988. Carbon monoxide poisoning. Br. Med. J. 296(6615):77–79.

Mihevic, P.M., J.A.Gliner. and S.M.Horvath. 1983. Carbon monoxide exposure and information processing during perceptual-motor performance. Int. Arch. Occup. Environ. Health 51 (4):355–363.

Mikulka, P.R.O'Donnell, P.Heinig, and J.Theodore. 1970. The effect of carbon monoxide on human performance. Ann. N.Y. Acad. Sci. 174(1):409–420.

Min, S.K. 1986. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide poisoning. Acta Psychiat. Scand. 73(1):80–86.

Mullin, L.S., and N.D.Krivanek 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotoxicology 3 (1):126–137.

Musselman, N.P., W.A.Groff, P.P.Yevich, F.T.Wilinski, M.H.Weeks, and F.W.Oberst. 1959. Continuous exposure of laboratory animals to low concentration of carbon monoxide. Aerosp. Med. 30:524–529.

NIOSH (National Institute for Occupational Safety and Health). 2000. Immediately Dangerous to Life and Health Concentration (IDLHs). [Online]. Available: http://www.cdc.gov/niosh/idlh/630080.html. [Updated October 28, 2000].

NRC (National Research Council). 1985. Carbon Monoxide. Pp.17–38 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Carbon Monoxide. Pp. 61–90 in Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

O'Donnell, R.D., P.Mikulka, P.Heinig, and J.Theodore. 1971. Low level carbon monoxide exposure and human psychomotor performance. Toxicol. Appl. Pharmacol. 18(3):583–589.

O'Hanlon, J.F. 1975. Preliminary studies of the effects of carbon monoxide on vigilance in man. Pp. 61–75 in Behavioral Toxicology, B.Weiss and G.Laties, eds. New York: Plenum Press.

Parving, H-H. 1972. The effect of hypoxia and carbon monoxide exposure on plasma volume and capillary permeability to albumin. Scand. J. Clin. Lab. Invest. 30(1):49– 56.

Peterson, J.E., and R.D.Stewart. 1970. Absorption and elimination of carbon monoxide by inactive men. Arch. Environ. Health 21(2):165–171.

Pirnay, F., J.Dujardin, R.Deroanne, and J.M.Petit. 1971. Muscular exercise during intoxication by carbon monoxide . J. Appl. Physiol. 31(4):573–575.

Plum, F., J.B.Posner, and R.F.Hain. 1962. Delayed neurological deterioration after anoxia. Arch. Intern. Med. 110:18–25.

Purser, D.A., and K.R.Berrill. 1983. Effects of carbon monoxide on behavior in monkeys in relation to human fire hazard. Arch. Environ. Health 38(5):308–315.

Putz, V.R., B.L.Johnson, and J.V.Setzer. 1976. Effects of CO on Vigilance Performance. Effects of Low-Level Carbon Monoxide on Divided Attention, Pitch Discrimination, and the Auditory Evoked Potential. DHEW (NIOSH) 77–124. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National Institute of Occupational Safety and Health.

Putz, V.R., B.L.Johnson, and J.V.Setzer. 1979. A comparative study of the effects of carbon monoxide and methylene chloride on human performance. J. Environ. Pathol. Toxicol. 2 (5):97–112.

Ramsey, J.M. 1973. Effects of single exposures of carbon monoxide on sensory and psychomotor response. Am. Ind. Hyg. Assoc. J. 34(5):212–216.

Raven, P.B., B.L.Drinkwater, R.D.Ruhling, N.Bolduan, S.Taguchi, J.Gliner, and S.M. Horvath. 1974. Effect of carbon monoxide and peroxyacetyl nitrate on man's maximal aerobic capacity. J. Appl. Physiol. 36(3):288–293.

Ray, A.M., and T.H.Rockwell. 1970. An exploratory study of automobile driving performance under the influence of low levels of carboxyhemoglobin. Ann. N.Y. Acad. Sci. 174(1):396–408.

Schulte, J.H. 1963. Effects of mild carbon monoxide intoxication. Arch. Environ. Health 7:524–530.

Shiotsuka, R.N., R.T.Drew, and R.W.Wehner. 1984. Carbon monoxide enhances development of hypertension in Dahl rats. Toxicol. Appl. Pharmacol. 76(2):225– 233.

Sievers, R.F., T.I.Edwards, and A.L.Murray. 1942. A Medical Study of Men Exposed to Measured Amounts of Carbon Monoxide in the Holland Tunnel for 13 Years. Public Health Bulletin No. 278. Washington, DC: U.S. Government Printing Office.

Spencer, P.S., and H.H.Schaumburg, eds. 2000. Experimental and Clinical Neurotoxicology, 2nd Ed. New York: Oxford University Press.

Stender, S., P.Astrup, and K.Kjeldsen. 1977. The effect of carbon monoxide on cholesterol in the aortic wall of rabbits. Atherosclerosis 28(4):357–367.

Stern, F.B., W.E.Halperin, R.W.Hornung, V.L.Ringenburg, and C.S.McCammon. 1988. Heart disease mortality among bridge and tunnel officers exposed to carbon monoxide. Am. J. Epidemiol. 128(6):1276–1288.

Stewart, R.D. 1975. The effect of carbon monoxide on humans. Annu. Rev. Pharmacol. 15:409–423.

Stewart, R.D. 1976. Proceedings: the effect of carbon monoxide on humans. J. Occup. Med. 18 (5):304–309.

Stewart, R.D., P.E.Newton, M.J.Hosko, and J.E.Peterson. 1973. Effect of carbon monoxide on time perception. Arch. Environ. Health 27(3):155–160.

Stewart, R.D., J.E.Peterson, E.D.Baretta, R.T.Bachand, M.J.Hosko, and A.A. Herrmann. 1970. Experimental human exposure to carbon monoxide. Arch. Environ. Health. 21(2):154–164.

Theodore, J., R.D.O'Donnell, and K.C.Back. 1971. Toxicological evaluation of carbon monoxide in humans and other mammalian species. J. Occup. Med. 13:242–255.

Thom, S.R. 1990. Carbon monoxide-mediated brain lipid peroxidation in the rat. J. Appl. Physiol. 68 (3):997–1003.

Thom, S.R. 1992. Dehydrogenase conversion to oxidase and lipid peroxidation in brain after carbon monoxide poisoning. J. Appl. Physiol. 73(4):1584–1589.

Vogel, J.A., and M.A.Gleser. 1972. Effect of carbon monoxide on oxygen transport during exercise. J. Appl. Physiol. 32(2):234–239.

Vogel, J.A., M.A.Gleser, R.C.Wheeler, and B.K.Whitten. 1972. Carbon monoxide and physical work capacity. Arch. Environ. Health 24(3):198–203.

Vyskocil, A., M.Tusl, and K.Zaydlar. 1986. The effect of carbon monoxide on hormone levels and organ weights in rats. J. Appl. Toxicol. 6(6):443–446.

WHO (World Health Organization). 1999. Pp. 1–18 in Carbon Monoxide, Environment al Health Criteria 213, 2nd Ed. Geneva: WHO.

Winneke, G., G.Fodor, and H.Schlipkoter. 1978. Carbon monoxide, trichloroethylene, and alcohol: reliability and validity of neurobehavioral effects. Pp. 461–469 in Multidisciplinary Perspectives in Even-Related brain Potential Research, Proceedings of the Fourth International Congress on Event-Related Slow Potentials of the Brain (EPICIV), Univ. of NC and U.S. EPA, Hendersonville, NC, April 4–10, 1976, D.P.Otto, ed. EPA-600/9–77–043. Research Triangle Park, NC: U.S. Environmental Protection Agency.

Wright, G., P.Randell, and R.J.Shephard. 1973. Carbon monoxide and driving skills. Arch. Environ. Health 27(6):349–354.

Zhang, J., and C.A.Piantadosi. 1992. Mitochondrial oxidative stress after carbon monoxide hypoxia in the rat brain. J. Clin. Invest. 90(4):1193–1199.

4

Chlorine

This chapter reviews the physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on chlorine. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine from exposure to chlorine gas and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposure (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to chlorine.

BACKGROUND INFORMATION

Chlorine is an abundant, naturally occurring halogen gas that does not occur in nature in its elemental state (Table 4–1). However, chlorine combines readily with inorganic and organic substances, with the exception of rare gases other than xenon), and nitrogen (Budavari 1989). When formed, chlorine is a diatomic gas with a pungent, suffocating odor. Chlorine can be formed if seawater makes contact with submarine batteries, and it therefore poses a health (survival) risk in a disabled submarine. To protect the health of submarine personnel until they can be rescued submarine escape action levels (SEALs) are needed to avoid

adverse health effects or degradation in crew performance following short-term exposures to chlorine. This chapter presents the available toxicity information on chlorine and the subcommittee's evaluation of the Navy's proposed SEALs.

TABLE 4–1 Chemical and Physical Properties

CAS number	7782–50–5
Molecular formula	Cl_2
Molecular weight	70.9
Color	Greenish-yellow
Odor	Suffocating
Odor threshold	0.2–0.4 ppm
Boiling point	–34.05°C
Melting point	–101.00°C
Density (water=1)	1.5649 at boiling point
Vapor density	1.4085 at 20°C
Solubility	Water, alkalies
Conversion factors	1 ppm=2.9 mg/m^3
25°C, 1 atm	1 mg/m^3=0.34 ppm

Abbreviations: CAS, Chemical Abstract Service. Source: Budavari (1989)

Chlorine is used in the manufacture of many products, as a bleaching compound for residential and commercial use, and as a biocide for municipal water and waste treatment (i.e., purifying and disinfecting water, detinning and dezincing iron) (Budavari 1989). It also was used as chemical-warfare agent in World War I (Withers and Lees 1987).

TOXICOKINETIC CONSIDERATIONS

There are few toxicokinetic studies of chlorine inhalation, and there have been no toxicokinetic studies on dermal exposure to chlorine.

Absorption

Absorption of chlorine is primarily via the upper respiratory tract. Chlorine is moderately soluble and, thereby, considered a Category I gas (EPA 1994). Because of its reactivity at localized sites, chlorine is not readily absorbed systemi

cally. Dermal absorption is possible, but that constitutes a secondary and minor route of exposure. Chlorine reacts with moisture in tissue, resulting in a release of hydrochloric and hypochlorous acids (Budavari et al. 1996; Perry et al. 1994). Nodelman and Ultman (1999a, b) used a bolus inhalation method to study the absorption and distribution of inhaled chlorine during a single breath. Five male and five female volunteers were exposed to chlorine by nose and mouth separately at a concentration of 3 ppm (parts per million). Chlorine was predominantly absorbed in the upper respiratory system (nasal passages, mouth, pharynx), regardless of administration route, with less than 5% of the inspired chlorine found beyond the upper airway and none found in the respiratory air spaces.

Distribution

Inhaled chlorine is predominantly retained in the upper respiratory tract (Nodelman and Ultman 1999a, b), and is a known irritant. At low doses (≤2.5 ppm for up to 2 h), approximately 95% of chlorine is effectively scrubbed in the upper respiratory tract. At higher concentrations, it reaches the lungs and can exert toxic effects (EPA 1994).

Metabolism and Disposition

There are no studies on the metabolism of chlorine after inhalation or dermal exposure. Chlorine gas reacts at the localized site, resulting in little absorption into the systematic blood system (Eaton and Klaassen 1996).

HUMAN TOXICITY DATA

There have been many studies of the toxicity of chlorine in exposed human populations. The subject was of interest during World War I, when chlorine was used as a weapon and the lethality of exposure was widely documented. But lethal concentrations in accidental exposures often are not documented so experimental animal studies must be used. Chlorine is detectable at low, nonlethal concentrations. It is an irritant to eyes, nose, and throat at concentrations less than 0.5 ppm for 4 h.

Data sources regarding the toxicity of chlorine include experimental studies with human volunteers and animals; accidentally exposed cohorts of workers, communities, or individuals; warfare studies; and epidemiologic occupational investigations. Each of these data sources is reviewed below and summarized in

the accompanying tables (Tables 4–2 to 4–5). The information in the tables reflects the spectrum of chlorine gas exposure signs and symptoms (ranging from localized irritation to pulmonary edema and death).

Experimental Studies

Studies of chlorine exposure in humans are detailed in Tables 4–2 and 4–3. Table 4–2 presents early attempts to determine thresholds for irritant effects, and it is restricted to studies that focused on the irritant effects of chloride. The quality of these early data is questionable because some studies did not provide enough information to support their conclusions (Fieldner et al. 1921, as cited in NIOSH 1976), some used a small number of test subjects (Matt 1889, as cited by NIOSH 1976), and some reported difficulties in maintaining constant concentrations of chlorine within the exposure chambers (Rupp and Henschler 1967, as cited in NIOSH 1976).

Table 4–3 presents findings from more recent studies that quantified exposure. Overall, they indicate that chlorine can be detected at concentrations as low as 0.5 ppm (possibly even lower) for 4 h and that it causes slight irritation of the eyes, nose, and throat (Anglen 1981). At higher concentrations, irritant effects are more pronounced, and there are effects on pulmonary function at 1 ppm, which can increase with duration (Rotman et al. 1983). The effects appear to be transient, resolving after exposure ceased.

Experimental data support the conclusion that chlorine has both lethal and nonlethal effects in humans. Death can occur at high doses, and various effects, such as choking, coughing, and reactive airway dysfunction are seen at intermediate concentrations. Lower, nonlethal doses are associated with symptoms such as localized irritation of the eyes, nose, and throat. There are no data available where people have been exposed to chlorine gas at concentrations of 1–5 ppm or greater for more than 8 h.

Accidental Exposures

Numerous studies have examined the effects of accidental exposure to chlorine, and reviews of those studies have been published as well (e.g., NIOSH 1976; NRC 1976; WHO 1982) and will not be repeated here. In most of those studies, exposure to chlorine was high albeit not quantified. Overall, the studies indicate that exposure to high concentrations of chlorine causes effects in the respiratory tract (e.g., pulmonary edema, pneumonia, and tracheobronchitis) that can result in death (Römcke and Evensen 1940, as cited in WHO 1982; Baader 1952, as cited in NIOSH 1976; Dixon and Drew 1968; Adelson and Kaufman 1971).

Withers and Lees (1985) used lethality data from animal and human studies in a probit analysis to estimate concentrations that would be lethal to 50% (LC_{50}) or to 10% (LC_{10}) of a human population. They estimated a 30-min LC_{50} of 250 ppm for a normal population, 100 ppm for a susceptible population, and 210 ppm for the average population (combining normal and susceptible groups). The estimated LC_{10} for each population was 125 ppm, 50 ppm, and 80 ppm, respectively.

TABLE 4–2 Threshold Data on Chlorine from Older Experimental Studies Using Human Subjects

Odor Detection (ppm)	Ocular Irritation (ppm)	Nasal Irritation (ppm)	Throat Irritation (ppm)	Cough (ppm)	Reference
1.3	1.3–2.5	3.5	2.5	3.5	Matt 1889 (as cited in NIOSH 1976)
3.5	—	—	15.1	30.2	Fieldner et al. 1921 (as cited in NIOSH 1976)
3.3	—	—	6.6	—	Vedder and Sawyer 1924 (as cited in NRC 1976)
0.044	—	0.09	0.09	0.09	Beck 1959 (as cited in NIOSH 1976)
0.2	0.2	0.2	0.2	0.2	Beck 1959 (as cited in NIOSH 1976)
0.3	1	1	1	1	Takhiroy 1960a,b (as cited in NRC 1976)
0.28–0.45	—	—	—	—	Ryazanov 1962
	0.45	0.06	0.058	0.5	Rupp and Henschler 1967 (as cited in NIOSH 1976)

Immediate effects of exposure to chlorine include choking, coughing, dyspnea, nausea, vomiting, anxiety, loss of consciousness, and eye and nasal irritation (Abhyankar et al. 1989; Beach et al. 1969; Chasis et al. 1947; Moulick et

al. 1992; Shroff et al. 1988). Subjects who survive exposure to high concentrations (>100 ppm) or who are exposed to lower concentrations (30–60 ppm) exhibit labored breathing, airway obstruction, pulmonary edema, impaired pulmonary function, tracheobronchitis, pneumonia, cyanosis, and cough (Chasis et al. 1947; Colardyn et al. 1976; Joyner and Durel 1962, as cited in WHO 1982; Kaufman and Burkons 1971; Kowitz et al. 1967; Ploysongsang et al. 1982). Some investigators have found that the effects can persist for months or years (Kaufman and Burkons 1971; Kowitz et al. 1967; Schwartz et al. 1990; Sessa et al. 1970, as cited in WHO 1982); others have found no significant permanent damage (Faure et al. 1970, as cited in WHO 1982; Jones et al. 1986; Weill et al. 1969).

There also are case reports of reactive airways dysfunction syndrome (RADS) associated with chlorine exposure (Alberts and do Pico 1996; Donnelly and FitzGerald 1990; Schönhofer et al. 1996). RADS is persistent hyper-reactivity of the airways that occurs after a single exposure to a high concentration of an irritant gas (Brooks et al. 1985). All reported RADS cases have resulted from accidental exposures in which exposure concentrations can be presumed to have been high.

Schwartz et al. (1990) followed 20 accidentally exposed individuals for 12 yr and reported an increasing prevalence of low residual volume over time and an increase in airway reactivity. These findings suggest that acute exposure has long-term pulmonary sequella and that the presence of air trapping indicates long-term injury. Unfortunately, the chlorine exposure was not quantified.

Other effects that have been reported after accidental exposure to chlorine, include palpable and painful liver (Tatarelli 1946, as cited in WHO 1982); anxiety, phobias, or hysteria (Chasis et al. 1947; Segaloff 1961, as cited in WHO 1982); electrocardiographic abnormalities (Leube and Kreiter 1971, as cited in WHO 1982); leukocytosis and elevated glutamate-pyruvate-transaminase (Leube and Kreiter 1971, as cited in WHO 1982); and brain hemorrhages (Baader 1952, as cited in NIOSH 1976).

Table 4–3 summarizes some studies for which there are quantitative data on accidental exposure.

The data from accidental chlorine exposure support the conclusion that dose is related to type and severity of health effect, which can range from localized irritation of the eyes, nose, and throat; to life-threatening respiratory symptoms that include pulmonary edema and pneumonia; to death.

TABLE 4-3 Human Toxicity Data, Exposure to Chlorine

Sample (n)	Route	Concentration (ppm)	Duration	Effect	Reference
EXPERIMENTAL STUDIES: Volunteers					
3	Whole body	0.21-0.52	NR	Investigators examined chlorine's effect on chronaxie, the minimum time need to excite a tissue with a current twice the rheobasic strength, and on reactions to visual stimulus. Prolonged optical chronaxie was found at 0.52 ppm, but not between 0.21 and 0.34 ppm. Optical chronaxie values returned to baseline levels within 2-2.5 min after exposure ceased. Increased sensitivity to light was found at 0.52 ppm, but not at 0.28 ppm. NIOSH (1976) noted that this study measured fine alterations in physiology and their importance to human health is poorly understood.	Takhirov 1960b (as cited in NRC 1976)
8	Whole body	0.5, 1, 2, 4.0	2 h	No complaints at 0.5 or 1 ppm. At 2 ppm, subjects reported slight irritation of the eyes, nose, throat. At 4 ppm, subjects reported objectionable odor, irritation of the nose and throat, desire to cough. No effects on lung function between 0.5 and 2 ppm. Only 2-3 subjects exposed at 4 ppm remained in the exposure chamber for 2 h, so lung function was not reported for that group.	Joosting and Verberk 1974

Sample (n)	Route	Concentration (ppm)	Duration	Effect	Reference
31	Whole body	0.5, 1, 2.0	4 h	At the two lower concentrations, subjects detected odor and reported throat irritation and an urge to cough. At 2 ppm, effects were reported to be more irritating.	Anglen 1981
8	Whole body	0.5, 1.0	8 h (with 30-min or 1-h break for testing after 4 h)	Pulmonary function tests were performed at 4 and 8 h. At 4 h, small but statistically significant changes were observed at 1 ppm, including changes in FEV_1, PEFR, FEF_{50}, and FEF_{25}, TLC, Raw, and difference in nitrogen concentration. At 8 h, there were alterations in forced vital capacity, FEV_1, PEFR, FEF_{50}, FEF_{25}, and Raw. Most of these values returned to normal the next day.	Rotman et al. 1983
WARFARE EXPOSURE STUDIES: Soldiers					
700	Whole body	NR	NR	Review of medical records of soldiers gassed with chlorine. Acute effects included death, dyspnea, pulmonary edema, bronchitis, pneumonia, asthma. Long-term effects (4 yr after exposure) included "irritable heart" (condition not described). There appeared to be no correlation between acute pulmonary effects and health status 4 yr later.	Meakins and Priestly 1919
838 (from 1,843 casualities)	Whole body	NR	NR	Review of medical records 8-10 yr after exposure. 4 deaths attributed to "later effect of chlorine gasing." Subjects had bronchopneumonia, lobar pneumonia, purulent pleurisy, tubercular	Gilchrist and Matz 1933

				meningitis. Survivors exhibited pulmonary tuberculosis, bronchitis, pleurisy, neurocirculatory asethnia, tachycardia, dyspnea, nephritis, laryngitis, valvular heart disease, keratitis, conjunctivitis. Most subjects made complete recovery. 9 subjects had long-term effects, such as pulmonary tuberculosis, bronchitis, chronic adhesive pleurisy.	
	Whole body	10-1,000	NR	Investigators concluded that chlorine is subjectively identified at 10 ppm, produces slight effects at 20 ppm, and causes death at 1,000 ppm within 5 min. "Asphyxiating phase" occurs up to 36 hr after exposure and includes irritation of the throat, coughing, dyspnea, aphonia, bardycardia, pulsus tardus, cyanosis, subnormal temperature. Death during this phase was attributed to pulmonary edema. "Post-asphyxiating phase" occurs when pulmonary edema subsides and bronchitis develops. Other effects include headache, nausea, vomiting, weakness, diarrhea.	Gerchik 1939
ACCIDENTAL EXPOSURE STUDIES					
85	Whole body	30-60 (Estimated)	NR	Acute effects included cough, dyspnea, expectoration, respiratory problems. Some of the more severe effects were death, pulmonary edema, bronchopneumonia. Effects were more severe in individuals undergoing physical exertion. Most reported chronic effect was dyspnea.	Römcke and Evensen 1940 (as cited in WHO 1982); Hoveid 1956 (as cited in NRC 1976)

Sample (n)	Route	Concentration (ppm)	Duration	Effect	Reference
100 (65 casualities, with 15 hospital-ized)	Whole body	10-400	NR	1 death and 10 cases of pulmonary edema. Subjects exhibited dyspnea, coughing, vomiting, eye irritation, and burns of the face. Chest X-rays of hospitalized patients showed fine miliary mottling of the lungs. No evidence of pneumonitis, and findings disappeared 12 d after exposure.	Joyner and Durel 1962
				Hysteria after exposure reported, particularly among individuals with "slight tendencies toward neurosis." 1 physician reported cases of congestive heart failure in elderly subjects; all responded to treatment.	Segaloff 1961 (as cited in WHO 1982)
				7-yr follow-up of the 12 most severely affected subjects indicated no permanent lung damage.	Weill et al. 1969
88 (25 with prior exposure at lower doses)	Whole body	66 ppm	NR	Immediate effects included dyspnea, coughing, irritation of the eyes and throat, headache, giddiness, chest pain, abdominal discomfort. Subjects also exhibited hilar congestion, bronchial vasculature markings, respiratory incapacitation, tracheobronchial congestion, chronic bronchitis, scattered hemorrhages, bronchial erosion. Bronchial smears taken from 28 subjects 5 d after exposure showed basal-cell and goblet-cell hyperplasia, acute inflammation, and chromatolysis	Shroff et al. 1988

				of columnar epithelial cells. 15 subjects exhibited columnar epithelial cell syncitia, nonpigmented alveolar macrophages, and proliferating fibroblasts and capillary fragments. Evidence of epithelial regeneration and repair by fibrosis 15-25 d after exposure.	
14	Whole body	30 ppm	NR	5 subjects had pre-existing COAD. Immediate effects in all subjects included lacrimation, sneezing, coughing, sputum, retrostenal burning, dyspnea, apprehension, vomiting. Among non-COAD subjects, all effects disappeared within 2 wk and pulmonary function was normal at 6 mo. Among COAD subjects, effects persisted and there was no improvement in pulmonary function at 6 mo.	Abhyankar et al. 1989
82	Whole body	66 ppm (found 2 h after leak)	<1 h	All subjects exhibited dyspnea, cough, bronchospasm. Other effects included irritation of the eyes and throat, headache, abdominal pain, vomiting, giddiness. 5 subjects had cyanosis, X-rays showed cases of patchy infiltrates, hilar congestion. Pulmonary function was affected in most subjects; bronchoscopy revealed tracheobronchial mucosal irritation. Some subjects had hemorrhagic spots, erosions, ulcers. In a follow-up of 16 patients for 1 yr, 4 reported	Moulick et al. 1992

Sample (n)	Route	Concentration (ppm)	Duration	Effect	Reference
				persistent cough 4-6 wk after discharge from the hospital. No symptoms were found in any subject after 1 yr, chest X-rays and pulmonary function tests were normal. In a follow-up of 5 subjects for 3 yr, no residual symptoms were found.	
OCCUPATIONAL EPIDEMIOLOGY STUDIES					
15	Whole body	NR	NR	Pregnancy outcome of 15 female workers tracked between 1932 and 1933. 2 subjects had miscarriages (1 appeared to be induced). The others had normal births. Investigators concluded the chlorine exposure had no effect on pregnancy, delivery, lactation.	Skljanskaja et al. 1935 (as cited in WHO 1982)
35	Whole body	NR	6.4 yr (average employ-ment)	Subjects reported suffering from respiratory diseases; no X-ray changes found.	Evans 1940 (as cited in NIOSH 1976)
49	Whole body	NR	12 yr (average employ-ment)	No statistically significant differences in measurements of hemoglobin, red blood cell counts, leukocyte counts between exposed workers and 39 non-exposed workers.	Tawast et al. 1956 (as cited in NIOSH 1976)
52 Workers in mercury-	Whole body	<0.37	10 yr (mean employ-	All subjects had periodic short-term exposure to high concentrations of chlorine. Respiratory function and prevalence of chronic lung disease	Capodaglio et al. 1969 (as cited in WHO 1982)

cell chlorine production unit			ment)	not statistically different from 27 unexposed employees.	
139 Chlorine gas workers	Whole body	<1.0 (average)	NR	Short-term exposure to high concentrations of chlorine combined with occasional long-term exposure to low concentrations might be associated with decreased maximum midexpiratory flow; long-term exposure to low concentrations of chlorine did not appear to have such an association.	Chester et al. 1969
332 Chlorine plant workers (382 control workers)	Inhalation and dermal	0.006-1.42	10.9 yr (average employment)	No statistically significant signs or symptoms observed on a dose-response basis, compared with 382 control workers, for abnormal chest X-rays, electrocardiograms, pulmonary function. Controls were age matched.	Patil et al. 1970
147 Pulp mill workers	Whole body	7.4, trace, and <0.001 in 1958, 1962, and 1963	NR	Pulp mill workers potentially exposed to chlorine, sulfur dioxide, chlorine dioxide, and/or hydrogen sulfide. 2 subgroups were exposed predominantly to chlorine/chlorine dioxide or sulfur dioxide. No significant differences observed between the subgroups and a nonexposed group of workers (paper mill).	Ferris et al. 1967

Sample (n)	Route	Concentration (ppm)	Duration	Effect	Reference
271 Workers (mortality study), 200 (morbidity study), pulp and paper mill	Whole body	7.4, trace, and <0.001 in 1958, 1962, and 1963	NR	10-yr follow-up mortality and morbidity study. No increased mortality, incidence of specific cause of death, respiratory symptoms, prevalence of chronic nonspecific respiratory disease. Some suggestion that exposure to chlorine or sulfur dioxide might have a slight adverse effect on pulmonary function.	Ferris et al. 1979

Abbreviations: COAD, chronic obstructive airway disease; FEF_{50}, forced expiratory flow rate at 50% vital capacity; FEF_{25}, forced expiratory flow rate at 25% vital capacity; FEV_1, forced expiratory volume at 1s; NR, not reported; PEFR, peak expiratory flow rate; Raw, airway resistance; TLC, total lung capacity.

Warfare Exposures

During World War I, chlorine gas was used as a weapon that was associated with a range of symptoms that depended upon concentration and duration of exposure. The spectrum of signs and symptoms reported varied from localized irritation to death.

Retrospective studies (see Table 4–3) of soldiers exposed to chlorine gas indicate that chlorine initially causes dyspnea, pulmonary edema, bronchitis, and pneumonia, which can result in death (Gilchrist and Matz 1933, as cited in Das and Blanc 1993; Meakins and Priestly 1919). Some subjects continued to suffer respiratory problems for years after exposure (Gilchrist and Matz 1933, as cited in Das and Blanc 1993).

Occupational and Epidemiological Studies

Table 4–3 presents details from occupational and epidemiologic studies of chlorine. In a review of the prevalence of chronic obstructive pulmonary disease among chlorine gas workers, Chester et al. (1969) reported that short-term exposure to high concentrations of chlorine combined with occasional long-term exposure to low concentrations might be associated with decreased maximum mid-expiratory flow; long-term exposure to low concentrations of chlorine did not appear to have such an association. However, the investigators did not provide any quantitative data on what constituted low or high concentrations. Another study found some evidence that chronic exposure to chlorine might have reduced pulmonary function in workers (Ferris et al. 1967, 1979), but others have not found differences between exposed and non-exposed workers (Capodaglio et al. 1969, as cited in WHO 1982; Patil et al. 1970).

The findings on the long-term effect of exposure—in particular, RADS and neurophysiologic and neuropsychologic effects—are equivocal. Clinical changes have been observed on x-rays, but not all studies have addressed other potential causes, such as cigarette smoking or unrelated occupational exposures.

EXPERIMENTAL ANIMAL TOXICITY DATA

Acute Exposures

Acute inhalation exposure to chlorine has been shown to cause lethal and nonlethal toxic effects in a variety of tests involving laboratory animals. Table 4–4

lists LC_{50} data for chlorine in rats and mice. Table 4–5 describes acute toxicity studies. In those studies, consistent effects were observed in the respiratory tract, including irritation of the mucosa of the respiratory passages, dyspnea, reduction in respiratory rate, and pulmonary edema. Chlorine can cause immediate or delayed death (Underhill 1920; Zwart and Woutersen 1988), and some investigators have shown that duration of exposure, as well as concentration, affects survival (Bitron and Aharonson 1978).

There are no animal toxicity studies specifically on dermal exposure to chlorine gas, but most of the inhalation studies involved whole-body exposures. Those studies reported irritation of the mucous membranes of the respiratory tract and the eyes.

Repeated Exposure

Repeated or continuous exposure to chlorine has been studied in several animal species (Table 4–5). As in acute studies, the primary effects are irritation of the respiratory tract (nasal passages, nasopharynx, larynx, trachea, lungs) and the eyes. In general, the severity of the effects was related to concentration and duration of exposure. No mortality or histopathologic effects in the respiratory tract below the nose have been observed in studies where rats, mice, or monkeys were exposed at concentrations of 2 to 3 ppm for 6 h/d, 5 d/wk for 6 wk (Barrow et al. 1979; Klonne et al. 1987; Wolf et al. 1995). However, 3 of 20 rats died in a group of rats exposed to 9 ppm, 6 h/d, 5 d/wk for 6 wk All of the rats in this group also had marked histopathologic lesions in larynx, trachea, and lung (Barrow et al. 1979). Jiang et al. (1983) reported that rats exposed at a concentration of 9.1 ppm for 6 h/d for 1, 3, or 5 d had lesions in the nasal passages and minor changes to the nasopharynx, larynx, trachea, and lungs.

MECHANISM OF ACTION

The irritation of the respiratory tract caused by chlorine is thought to be due to its strong oxidizing capacity. Chlorine oxidizes water in the surface tissues of the respiratory tract to form hydrochloric and hypochlorous acids, which break into hydrochloric acid (HCl) and free oxygen. When combined with water, oxygen radicals are released, resulting in tissue destruction enhanced by the presence of HCl (Perry et al. 1994; Stokinger 1981; Wolf et al. 1995). Nascent oxygen is a potent protoplasmic poison.

TABLE 4–4 LC50 for Exposure to Chlorine

Species	Duration	LC_{50} (ppm)	Reference
Rat	5min	5,500	Zwart and Woutersen 1988
	10 min	1,946	Zwart and Woutersen 1988
	30min	700	Zwart and Woutersen 1988
	53 min	1,000	Weedon et al. 1940 (as cited in WHO 1982)
	60 min	455	Zwart and Woutersen 1988
	60 min	293	Vernot et al. 1977
	408 min	250	Weedon et al. 1940 (as cited in WHO 1982)
Mouse	10 min	523	Silver and McGrath 1942 (as cited in WHO 1982)
	10 min	594	Silver and McGrath 1942 (as cited in WHO 1982)
	10 min	626	Geiling and McLean 1941 (as cited in WHO 1982)
	10 min	674	Silver et al. 1942 (as cited in WHO 1982)
	10 min	1,057	Zwart and Woutersen 1988
	11 min	290	Bitron and Aharonson 1978
	28 min	1,000	Weedon et al. 1940 (as cited in WHO 1982)
	30 min	504	Zwart and Woutersen 1988
	30 min	127	Schlagbauer and Henschler 1967 (as cited in WHO 1982)
	55 min	170	Bitron and Aharonson 1978
	60 min	137	Vernot et al. 1977
	408 min	250	Weedon et al. 1940 (as cited in WHO 1982)

Abbreviations: LC_{50}, median lethal concentration.

NAVY'S RECOMMENDED SEALS

The Navy proposed a SEAL 1 of 2 ppm and a SEAL 2 of 5 ppm for chlorine. These values appear to be based primarily on information presented in a

TABLE 4-5 Experimental Animal Toxicity Data, Exposure to Chlorine

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
ACUTE EXPOSURE						
Rat: 4	Whole body	50, 100, 200, 500, 1,500	2-10 min	At concentrations ≤ 500 ppm, no significant histologic changes in airway mucosa or lungs. At 1,500 ppm for 2 min, slight perivascular edema, occasional small clusters of polymorphonuclear leukocytes in mucosa of large airways. For 10-min exposure, airspace and interstitial edema 1 h after exposure, decreased edema and appearance of mucosa polymorphonuclear leukocytes at 5-24 h, and epithelial regeneration at 72 h.	NOAEL: 500	Demnati et al. 1995
Rat: 10	Whole body	322-5,793	5 min-1 h	Clinical effects observed in this study to determine the LD_{50} included restlessness, eye and nasal irritation, dyspnea, reduced respiratory rate. At 5,793 ppm for 5 min and 2,248 ppm for 10 min, pathologic changes observed in nose, larynx, trachea. No deaths at 547 ppm for 30 min or at 322 ppm for 60 min.	NA	Zwart and Wourtersen 1988
Rat: 40-50	Whole body	25	10 min	50% reduction in respiratory rate.	NA	Barrow and Steinhagen 1982

Rat: 14	Whole body	10.9	6 h	50% reduction in respiratory rate.	NA	Chang and Barrow 1984
Mouse: 8	Whole body	1,500	5 min	Lung resistance increased up to 3 d after exposure. Responses to methacholine enhanced for up to 7 d after exposure. Effects persisted in some rats for a month or more. Histopathologic changes included epithelial flattening, necrosis, increase in smooth muscle mass, epithelial regeneration. Bronchoalveolar lavage revealed increased number of neutrophils. The most damage to the epithelium occurred within 1-3 d of exposure, corresponding with maximal functional changes.	LOAEL: 1500	Demnati et al. 1998
Mouse: 4	Whole body	0.7-38.4	10 min	50% reduction in respiratory rate at 9.3 ppm.	NA	Barrow et al. 1977
Mouse: 10	Whole body	579-1,654	10 min	Deaths during second week of observation, suggesting that they might have been due to secondary infection. No deaths at 754 ppm.	NA	Zwart and Woutersen 1988
Mouse: 10	Whole body	458-645	30 min	Some deaths occurred during second week of observation, suggesting that they might have been due to secondary infection.	NA	Zwart and Woutersen 1988

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Mouse: 10	Whole body	3.5	60 min	50% reduction in respiratory rate occurred within 10 min of exposure.	NA	Gagnaire et al. 1994
Mouse: 28-84	Whole body	170, 290	15-160 min and 5-30 min, respectiv ely	Duration of exposure affected survival. At 290 ppm, mortality was 100% at 25 min, 80% at 15 min, 40% at 9 min, and 0% for 6 min. At 170 ppm, mortality was 80% at 120 min, 50% at 52 min, and 10% at 22 min. Consistent delay of 5-10 d before substantial mortality.	NA	Bitron and Aharonson 1978
Mouse: 10	Whole body	10	3 h	8 deaths within 4 d. Pathologic examinations revealed pulmonary edema and necrosis, inflammation of the respiratory epithelium.	NA	Schlagbauer and Henschler 1967 (as cited in WHO 1982)
Guinea pig: NR	Whole body	NR	15-30 min	No data on mortality presented. Animals reported to have pulmonary edema, hemorrhages.	NA	Faure et al. 1970 (as cited in WHO 1982)
Rabbit: 4	Whole body	50, 100, 200	30 min	Lung measurements of volume-pressure relationships and inspiratory-expiratory flow rate taken periodically between 30 min and 60 d after exposure. No effects observed at 50 ppm. Alterations in flow rate ratios observed at 100 ppm and 200 ppm, recovered after 14 and 60 d,	NOAEL: 50 LOAEL: 100	Barrow and Smith 1975

				respectively. Pulmonary compliance compromised throughout the study. Pathologic changes of lungs included hemorrhages, pneumonitis, anatomic emphysema at 3 and 14 d after exposure, but not after 60 d.		
Dog: <100	Whole body	50-2,000	30 min	"Minimum acute lethal toxicity" for 3-d observation, 800-900 ppm. At 50-250 ppm, some delayed deaths occurred after the 3-d period. At the higher concentrations, immediate effects included respiratory arrest and bronchoconstriction. After exposure ceased, gradual increase in respiratory rate for 1 h, subsided after 17 h. Pulse rate declined initially, but doubled over the normal rate after 10 h. Animals that died had pulmonary edema. Other clinical effects included ocular irritation, sneezing, salivation, retching, vomiting, general excitement, dyspnea, respiratory distress. Pathologic examination revealed necrosis of the epithelial lining of the respiratory tract, pneumonia, bronchitis, bronchiolitis, and fibrosis.	NA	Underhill 1920 (as cited in WHO 1982); Winternitz et al. 1920 (as cited in WHO 1982)
Pig: 2-6	Trach. tube	110, 140 (50 or 100 L)	6 h	Pigs were anesthetized and mechanically ventilated. At 140 ppm (100 L), severe	LOAEL: 110	Gunnarsson et al. 1998

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
				pulmonary dysfunction occurred after 10 min. 5 of 6 died within 6 h. Pigs exhibited rapid drop in arterial oxygen tension, biphasic decline in lung complance, gradual increase in cardia output. Similar but milder effects observed at the lower concentration; evidence of improvement in those effects at the end of the study. Microscopic examinations revealed epithelial sloughing of the bronchi and bronchioles, infiltration with leukocytes.		
REPEATED EXPOSURE						
Rat: 9-10	Whole body	9.1	6 h/d for 1, 3, or 5 d	Pathologic exams performed immediately after exposure revealed lesions in the nasal passages, including epithelial degeneration with epithelial cell exfoliation, erosion, ulceration (respiratory epithelium) and epithelial erosion and ulceration of the olfactory epithelium of the dorsal meatus. Less severe changes were observed in the nasopharynx, larynx, trachea, lungs.	LOAEL: 9.1	Jiang et al. 1983
Rat (SPD): 10	Whole body	16	1 h/d for 4 wk or 2	Animals exhibited inflammatory changes of the trachea and bronchi that resulted in		Elmes and Bell 1963 (as cited

			h/d for 5 wk	bronchitis and death.		in WHO 1982)
Rat: 20	Whole body	1, 3, 9	6 h/d, 5 d/wk for 6 wk	At 9 ppm: 3 deaths, irritation of the eyes and upper respiratory tract, dyspnea, decreased body weight gain, increased segmented neutrophils and hematocrit, increased specific gravity of the urine, increased serum enzymes and urea nitrogen. Pathologic changes included inflammatory responses in the upper and lower respiratory tract; ulceration, erosion, edema, hemorrhage of the gastric mucosa; minor renal tubular and hepatocellular cytoplasmic changes. At 3 ppm: Irritation of the eyes and upper respiratory tract, decreased body weight gain, increased urine specific gravity. Pathologic changes included inflammation of the respiratory tract, minor hepatocellular cytoplasmic changes. At 1 ppm: Slight irritation of the nasal mucosa and decrease in body weight in females; increased urine specific gravity. Less severe pathologic evidence of inflammation of the respiratory tract.	LOAEL: 1	Barrow et al. 1979

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Rat (SPF): 15	Whole body	40	3 h/d for a total of 42 hr	Clinical effects included coughing, sneezing, and runny and blood-stained noses. Histologic examinations 14 d after exposure revealed recovery.	LOAEL: 40	Bell and Elmes 1965
Rat (SPF and SPD): 8	Whole body	90,104	3 h/d for 6 or 20 d	Mortality, pulmonary inflammation, emphysema, pneumonia. Effects were more severe in SPD rats.		Bell and Elmes 1965
Rat: 140	Whole body	0.4, 1.0, 2.5	6 h/d, 5 d/wk or 3 alternate d/wk for 2 yr	Lesions in nasal passages of all animals (mainly the anterior nasal cavity) included respiratory and olfactory epithelial degeneration, septal fenestration, mucosa inflammation, respiratory epithelial hyperplasia, squamous metaplasia, goblet cell hypertrophy and hyperplasia, secretory metaplasia of the transitional epithelium of the lateral meatus. Severity of the lesions was concentration related.	LOAEL: 0.4	Wolf et al. 1995
Mouse: NR	Whole body	2.5, 5.0	8 h/d for 3 d	Animals exhibited loss of body weight. At 5.0 ppm, microscopic changes found in lungs. Investigators did not report examination of lungs of animals exposed to the lower concentration.	LOAEL: 5.0	Schlagbauer and Henschler 1967 (as cited in WHO 1982)

Mouse: 24-34	Whole body	9.3	6 h/d for 5 d	Lesions found in anterior respiratory epithelium adjacent to the dorsal meatus and in respiratory epithelium, included exfoliation, inflammation erosion, ulceration, necrosis. Tracheal lesions and terminal bronchiolitis, with occlusion of the affected bronchioles by serocellular exudate. Recovery minimal to moderate after 72 h.	LOAEL: 9.3	Buckley et al. 1984
Guinea pig: NR	Whole body	1.7	5 h/d for 87 d	Some animals pre-exposed to tubercle bacilli, others were not. Deaths occurred among pre-exposed animals.	LOAEL: 1.7	Arloing et al. 1940 (as cited in WHO 1982)
Dog: 4	Whole body	24-30	30 min	Clinical signs included lacrimation, salivation, retching, vomiting. Variable effects on pulse, respiratory rate, increases in body temperature.	LOAEL: 24	Barbour 1919 (as cited in NIOSH 1976)
Dog: 3	Whole body	180-200	30 min	Clinical signs included lacrimation, salivation, retching, vomiting, reduction in muscle activity, dyspnea. Slight decrease in body temperature. No evidence of bronchitis or pulmonary edema.	LOAEL: 180	Barbour 1919 (as cited in NIOSH 1976)
Dog: NR	Whole body	800-900	30 min	85% mortality. Decreases in body temperature. Surviving animals unable to regulate body temperature when exposed to high or low external temperatures.	NA	Barbour 1919 (as cited in NIOSH 1976)

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Monkey: 4	Whole body	0.1, 0.5, 2.3	6 h/d, 5 d/wk for 1 yr	At the highest concentration, the only significant clinical effect observed was ocular irritation. Histopathologic examinations revealed changes in nasal passages and trachea of a few animals, including focal epithelial hyperplasia with loss of cilia, decreased number of goblet cells. A few of the animals exposed to 0.5 pm had mild lesions in the nasal passages.	NOAEL: 0.5 LOAEL: 2.3	Klonne et al. 1987

Abbreviations: LD_{50}, median lethal dose; LOAEL, lowest observable adverse effect level; NOAEL, no observed adverse effect level; NR, not reported; ppm, parts per million; SPD, spontaneous pulmonary disease; SPF, specific pathogen-free.

review of the toxicity of chlorine (NRC 1976) which reported that men can work uninterrupted when exposed at 1–2 ppm, and that severe irritation of the eyes, nose, and respiratory tract is observed after a few minutes of exposure to 5 ppm.

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Table 4–6 presents exposure limits for chlorine recommended by other organizations. The 24-h emergency exposure guidance level (EEGL) is the most relevant guidance level to compare to the SEALs (NRC 1984). EEGLs were developed for healthy military personnel in emergency situations. An important difference between EEGLs and SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for EEGLs. Therefore, SEAL values are higher than the corresponding EEGL values.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's recommended SEAL 1 of 2 ppm for chlorine is too high. The subcommittee recommends a SEAL 1 of 1 ppm. The subcommittee recognizes that the dose-response curve for chlorine is steep and therefore, the margin of safety is narrow. The subcommittee's conclusion is based on studies in which human volunteers exposed to chlorine at a concentration of 0.5–4 ppm for 2–8 h complained or irritation of the eyes, nose, and throat (Joosting and Verberk 1974; NRC 1976; Anglen 1981; Rotman et al. 1983). Volunteers exposed at a concentration of 1 ppm for 8 h had transient pulmonary function changes; however, volunteers exposed at a concentration of 0.5 ppm for 8 h had only trivial pulmonary function changes (Rotman et al. 1983). The SEAL 1 is further supported by a study in which monkeys exposed to chlorine at 2 ppm for 6 h/d, 5 d/wk for 1 yr exhibited no histopathologic lesions of the lower respiratory tract (Klonne et al. 1987). That study would indicate that the recommended SEAL 1 has some margin of safety even if the exposure to chlorine lasts for 10 d.

TABLE 4–6 Exposure Recommendations from Other Organizations

Organization	Type of Exposure Recommendation	Exposure Limit, ppm	Reference
ACGIH	TLV-TWA (8 h/d during 40-h workweek)	0.5	ACGIH 1999
	TLV-STEL (15 min)	1	
AIHA	ERPG-1	1	AIHA 2001
	ERPG-2	3	
	ERPG-3	20	
DFG	MAK (8 h/d during 40-h workweek)	0.5	DFG 1997
	Peak Limit (5 min maximum duration, 8 times per shift)	1	
NAC	Proposed 8-h AEGL-1	0.5	Federal Register October 30, 1997. 62(210):58839–58851.
	Proposed 8-h AEGL-2	0.71	
	Proposed 8-h AEGL-3	7.1	
NIOSH	REL-TWA (10 h/d during 40-hr workweek)	0.5	NIOSH 2001
	IDLH	10	
NRC[a]	EEGL (1 h)	3	NRC 1984
	EEGL (24 h)	0.5	
	CEGL (90 d)	0.1	
OSHA	PEL-TWA (ceiling value)	1	OSHA 1999[b]

[a]Guidelines were established for use by the military.

[b]Occupational Safety and Health Standards. Code of Federal Regulations. Part 1910. 1000 Air Contaminants.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; AIHA, American Industrial Hygiene Association; CEGL, continuous exposure guidance level; DFG, Deutsche Forschungsgemeinschaft; EEGL, emergency exposure guidance level; ERPG, emergency response planning guidelines; IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; NAC, National Advisory Committee; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; STEL, short-term exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 5 ppm for chlorine is too high. The subcommittee recommends a SEAL 2 of 2.5 ppm for chlorine. That recommendation is supported by a study in which 3 human volunteers exposed to chlorine at a concentration of 4 ppm for 2 h were able to tolerate the exposure and volunteers exposed at a concentration of 2 ppm for 2 h did not have significant changes in lung function (Joosting and Verberk 1974). The subcommittee's recommended SEAL 2 is also supported by the study by Klonne et al. (1987), which is described above. The subcommittee concludes that most crew members should be able to tolerate the irritant effects of chlorine exposure at concentrations below 2.5 ppm for 24 h.

DATA GAPS AND RESEARCH NEEDS

Additional studies on the toxicity of chlorine in experimental animals are needed to better define the health effects of exposure at concentrations of 0.5–4 ppm, 24 h/d for up to 10 d. These studies should include evaluation of short-term effects, on pulmonary function and on long-term effects such as inflammation of the respiratory tract and pulmonary fibrosis. Studies are also needed on the interactive effects of chlorine with other gases found in disabled submarines.

Additional studies on chlorine toxicity in animals and, possibly, on human volunteers are needed to better define the health effects of chlorine gas exposure at 0.5–5 ppm, 24 h/d up to 7–10 d. Long-term exposure data for humans and animals is needed to approximate a disabled submarine situation. These studies should include evaluation of short-term effects on pulmonary function and long term effects such as pulmonary fibrosis. As is the case for all irritant toxic gases reviewed in this report.

REFERENCES

Abhyankar, A., N.Bhambure, N.N.Kamath, S.P.Pajankar, S.T.Nabar, A.Shrenivas, A.C.Shah, and S.N.Deshmukh. 1989. Six month follow-up of fourteen victims with short-term exposure to chlorine gas. J. Soc. Occup. Med. 39(4):131–132.

ACGIH (American Conference of Governmental Industrial Hygienists). 1999. TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents. Biological Exposure Indices. Cincinnati, OH: ACGIH.

Adelson, L., and J.Kaufman. 1971. Fatal chlorine poisoning: Report of two cases with clinicopathologic correlation. Am. J. Clin. Pathol. 56(4):430–442.

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Alberts, W.M., and G.A.do Pico. 1996. Reactive airways dysfunction syndrome. Chest 109(6):1618–1626.

Anglen, D.M. 1981. Sensory Response on Human Subjects to Chlorine in Air. PhD. Dissertation. University of Michigan.

Arloing, F., E.Berthet, and J.Viallier. 1940. Action of chronic intoxication by low concentration chlorine fumes on experimental guinea pigs. [in French]. Presse Med. 48:361.

Baader, E.W. 1952. Chlorine anhydride poisoning (the Walsum disaster). [in Spanish]. Med. Deporte Trab.17:5252, 5254, 5256, 5258–5259.

Barbour, H.G. 1919. The effects of chlorine upon the body temperature. J. Pharmacol. Exp. Ther. 14:65–73.

Barrow, C.S., and R.G.Smith. 1975. Chlorine induced pulmonary function changes in rabbits. Am. Ind. Hyg. Assoc. J. 36:398–403.

Barrow, C.S., and W.H.Steinhagen. 1982. Sensory irritation tolerance development to chlorine in F-344 rats following repeated inhalation. Toxicol. Appl. Pharmacol. 65(3):383–389.

Barrow, C.S., Y.Alarie, J.C.Warrick, and M.F.Stock 1977. Comparison of the sensory irritation response in mice to chlorine and hydrogen chlorine. Arch. Environ. Health 32(2):68–76.

Barrow, C.S., R.J.Kociba, L.W.Rampy, D.G.Keyes, and R.R.Albee. 1979. An inhalation toxicity study of chlorine in Fischer-344 rats following 30 days exposure. Toxicol. Appl. Pharmacol. 49(1):77–88.

Beach, F.X., E.S.Jones, and G.D.Scarrow. 1969. Respiratory effects of chlorine gas. Br. J. Ind. Med. 26(3):231–236.

Beck, H. 1959. Pp. 1–7, 16–19, 21–31, 44–54 in Experimental Determination of the Olfactory Thresholds of Some Important Irritant Gases (Chlorine, Sulphur Dioxide, Ozone, Nitrous Gases) and Symptoms Induced in Humans by Low Concentrations, [in German]. Ph. D. Thesis. Universität Würzburg.

Bell, D.P., and P.C.Elmes. 1965. The effects of chlorine gas on the lungs of rats without spontaneous pulmonary disease. J. Pathol. Bacteriol. 89:307–317.

Bitron, M.D., and E.F.Aharonson. 1978. Delayed mortality of mice following inhalation of acute doses of CH_2O, SO_2, Cl_2, and Br_2. Am. Ind. Hyg. Assoc. J. 39(2):129– 138.

Brooks, S.M., M.A.Weiss, and I.L.Bernstein. 1985. Reactive airways dysfunction syndrome. Case reports of persistent airways hyperreactivity following high-level irritant exposures. J. Occup. Med. 27(7):473–476.

Buckley, L.A., X.Z.Jiang, R.A.James, K.T.Morgan, and C.S.Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. Toxicol. Appl. Pharmacol. 74 (3):417–429.

Budavari, S., ed. 1989. Pp. 323–324 in The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Ed. Rahway, NJ: Merck.

Budavari, S., M.J.O'Neil, A.Smith, P.E.Heckelman, and J.F.Kinneary. 1996. The

Merck Index, 12th Ed. Rahway, NJ: Merck.
Capodaglio, E., G.Pezzagno, G.C.Bobbio, and F.Cazzoli. 1969. Respiratory function test in workers employed in electrolytic production of chlorine and sodium. [in Italian]. Med. Lav. 60 (3):192–201.
Chang, J.C., and C.S.Barrow. 1984. Sensory irritation tolerance and cross-tolerance in F-344 rats exposed to chlorine or formaldehyde gas. Toxicol. Appl. Pharmacol. 76(2):319–327.
Chasis, H., J.A.Zapp, J.H.Bannon, J.L.Whittenberger, J.Helm, J.J.Doheny, and C.M. MacLeod. 1947. Chlorine accident in Brooklyn. Occup. Med. 4:152–176.
Chester, E.H., D.G.Gillespie, and F.D.Krause. 1969. The prevalence of chronic obstructive pulmonary disease in chlorine gas workers. Am. Rev. Resp. Dis. 99(3):365–373.
Colardyn, F., M.Van Der Straeten, J.Tasson, and J.Van Egmond. 1976. Acute chlorine gas intoxication. Acta Clin. Belg. 31(2):70–77.
Das, R., and P.D.Blanc. 1993. Chlorine gas exposure and the lung: A review. Toxicol. Ind. Health. 9 (3):439–455.
Demnati, R., R.Fraser, G.Plaa, and J.L.Malo. 1995. Histopathological effects of acute exposure to chlorine gas on Sprague-Dawley rat lungs. J. Environ. Pathol. Toxicol. Oncol. 14(1):15–19.
Demnati, R., R.Fraser, H.Ghezzo, J.G.Martin, G.Plaa, and J.L.Malo. 1998. Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats. Eur. Respir. J. 11(4):922–928.
DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, First Ed. Report No. 33. Weinheim: Wiley-VCH.
Dixon, W.M., and D.Drew. 1968. Fatal chlorine poisoning. J. Occup. Med. 10(5):249– 251.
Donnelly, S.C., and M.X.FitzGerald. 1990. Reactive airways dysfunction syndrome (RADS) due to chlorine gas exposure. Ir. J. Med. Sci. 159:275–277.
Eaton, D.L., and C.D.Klaassen. 1996. Principles of toxicology. Pp. 13–33 in Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th Ed. New York McGraw Hill.
Elmes, P.C., and D.Bell. 1963. The effects of chlorine gas on the lungs of rats with spontaneous pulmonary disease. J. Pathol. Bacteriol. 86:317–326.
EPA (U.S. Environmental Protection Agency). 1994. Chlorine. Integrated Risk Information system. [Online]. Available: http://www.epa.gov/ngispgm3/iris/subst/0405.htm (Last updated: May 5, 1998).
Evans, E.E. 1940. An X-ray study of the effects of industrial gases upon the human lung. Radiology 34(April):411–424.
Faure, J., M.Sibille, H.Faure, C.Stephan, M.Yacoub, and J.Motin. 1970. Acute chlorine and phosgene poisoning (clinical and experimental study). [in French]. Poumon Coeur 26 (8):913–929.
Ferris, B.G., W.A.Burgess, and J.Worchester. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br. J. Ind. Med. 24(1):26– 37.

Ferris, B.G., S.Puleo, and H.Y.Chen. 1979. Mortality and morbidity in a pulp and paper mill in the United States: A ten-year follow-up. Br. J. Ind. Med. 36(2):127–134.

Fieldner, A.C., S.R.Katz, and S.P.Kinney. 1921. Pp. 3–61 in Gas Masks for Gases Met in Fighting Fires. Tech. Paper 248. Washington, DC: U.S. Department of the Interior, Bureau of Mines.

Gagnaire, F., S.Azim, P.Bonnet, G.Hecht, and M.Hery. 1994. Comparison of the sensory irritation response in mice to chlorine and nitrogen trichloride. J. Appl. Toxicol. 14(6):405–409.

Geiling, E.M.K., and F.C.McLean. 1941. Progress Report on Toxicity of Chlorine Gas for Mice to Nov. 6, 1941. Office of Scientific Research and Development Report 286. U.S. National Defense Research Committee. 21 pp.

Gerchik, M. 1939. Medical experience of Americans with chemical poison gas during the World War. Protar. 5(11):173–179.

Gilchrist, H.L., and P.B.Matz. 1933. 1. Chlorine, 2. Mustard. Pp. 1–41 in The Residual Effects of Warfare Gases. Washington, DC: U.S. Government Printing Office.

Gunnarsson, M., S.M.Walther, T.Seidal, G.D.Bloom, and S.Lennquist. 1998. Exposure to chlorine gas: Effects on pulmonary function and morphology in anesthetized and mechanically ventilated pigs. J. App. Toxicol. 18(4):249–255.

Hoveid, P. 1956. The chlorine gas accident in Mjöndalen (Norway), January 26, 1940: An after investigation. [in Norwegian]. Nord. Hyg. Tid. 37:59–66.

Jiang, X.Z., L.A.Buckley, and K.T.Morgan. 1983. Pathology of toxic responses to the RD_{50} concentration of chlorine gas in the nasal passages of rats and mice. Toxicol. Appl. Pharmacol. 71(2):225–236.

Jones, R.N., J.M.Hughes, H.Glindmeyer, and H.Weill. 1986. Lung function after acute chlorine exposure. Am. Rev. Respir. Dis. 134(6):1190–1195.

Joosting, P., and M.Verberk. 1974. Emergency population exposure: A methodological approach. Pp. 2,005–2,029 in Recent Advances in the Assessment of Health Effects of Environmental Pollution, International Symposium Proceedings, Vol. 4. Commission of the European Communities, World Health Organization, U.S. Environmental Protection Agency. NTIS PB261 480.

Joyner, RE., and E.G.Durel. 1962. Accidental liquid chlorine spill in a rural community. J. Occup. Med. 4:152–154.

Kaufman, J., and D.Burkons. 1971. Clinical, roentgenologic and physiologic effects of acute chlorine exposure. Arch. Environ. Health 23(1):29–34.

Klonne, D.R., C.E.Ulrich, M.G.Riley, T.E.Hamm, Jr., K.T.Morgan, and C.S.Barrow. 1987. One-year inhalation toxicity study of chlorine in rhesus monkeys (Macaca mulatta). Fundam. Appl. Toxicol. 9(3):557–572.

Kowitz, T.A., R.C.Reba, R.T.Parker, and W.S.Spicer. 1967. Effects of chlorine gas upon respiratory function. Arch. Environ. Health 14(4):545–558.

Leube, G., and H.Kreiter. 1971. Acute chlorine poisoning. Case reports of 90 patients with acute poisoning, [in German]. Med. Klin. 66(10):354–357.

Matt, L. 1889. Experimental Contributions to the Theory of the Effects of Poisonous Gases on Human Beings, [in German]. Inaugural dissertation. Julius-Maximilliams-Universität, Würzburg.

Meakins, J.C., and J.G.Priestly. 1919. The after-effects of chlorine gas poisoning. Can. Med. J. 9:968–974.

Moulick, N.D., S.Banavali, A.D.Abhyankar, S.Borkar, J.Aiyengar, N.M.Kapadia, and R.C.Khokhani. 1992. Acute accidental exposure to chlorine fumes: A study of 82 cases. Indian J. Chest Dis. Allied Sci. 34(2):85–89.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard Occupational Exposure to Chlorine. HEW Pub. No. (NIOSH) 76–170. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 2000. Appendix A NIOSH Pocket Guide to Chemical Hazards. NIOSH Potential Occupational Carcinogens. [Online]. Available: http://www.cdc.gov/niosh/npg/nengapdx.htm. [April 30, 2001].

Nodelman, V., and J.S.Ultman. 1999a. Longitudinal distribution of chlorine absorption in human airways: Comparison of nasal and oral quiet breathing. J. Appl. Physiol. 86(6):1984–1993.

Nodelman, V., and J.S.Ultman. 1999b. Longitudinal distribution of chlorine absorption in human airways: A comparison to ozone absorption. J. Appl. Physiol. 87(6):2073– 2080.

NRC (National Research Council). 1976. Medical and Biological Effects of Environmental Pollutants Chlorine and Hydrogen Chlorine. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

Patil, L.R.S., R.G.Smith, A.J.Vorwald, and T.F.Mooney. 1970. The health of diaphragm cell workers exposed to chlorine. Am. Ind. Hyg. Assoc. J. 31(6):678–686.

Perry, W.G., F.A.Smith, and M.B.Kent. 1994. The Halogens. Pp. 4482–4505 in Patty's Industrial Hygiene and Toxicology, Vol. II, Part F. G.F.Clayton, and F.E.Clayton, eds. New York: John Wiley & Sons.

Ploysongsang, Y., B.C.Beach, and R.E.DiLisio. 1982. Pulmonary function changes after acute inhalation of chlorine gas. South Med. J. 75(1):23–26.

Römcke, O., and O.K.Evensen. 1940. The chlorine poisoning in Mjöndalen. [in Norwegian]. Nord. Med. 7:1224–1226.

Rotman, H.H., M.J.Fliegelman, T.Moore, R.G.Smith, D.M.Anglen, C.J.Kowalski, and J.G.Weg. 1983. Effects of low concentrations of chlorine on pulmonary function in humans. J. Appl. Physiol. 54(4):1120–1124.

Rupp, H., and D.Henschler. 1967. Effects of low chlorine and bromine concentrations on man. [in German]. Int. Arch. Arbeitsmed. 23(1):79–90.

Ryazanov, V.A. 1962. Sensory physiology as basis for air quality standards. Arch. Environ. Health 5:480–491.

Schlagbauer, M., and D.Henschler. 1967. Toxicity of chlorine and bromine in single and repeated inhalations. [in German]. Int. Arch. Arbeitsmed. 23(1):91–98.

Schönhofer, B., T.Voshaar, and D.Köhler. 1996. Long-term lung sequelae following accidental chlorine gas exposure. Respiration 63(3):155–159.

Schwartz, D.A., D.D.Smith, and S.Lakshminarayan. 1990. The pulmonary sequelae associated with accidental inhalation of chlorine gas. Chest 97(4):820–825.

Segaloff, L. 1961. Task Sirocco. Community Reactin to an Accidental Chlorine Exposure. Project Summit. Contract No. DA-18–064-Cml-2757. Philadelphia, PA: The Institute for Cooperative Research, University of Pennsylvania.

Sessa, T., L.Pecora, G.Vecchione, and R.Mole. 1970. The cardiorespiratory function in bronchopneumopathies caused by irritant gases. [in French]. Poumon Coeur 26(9):1097–1107.

Shroff, C.P., M.V.Khade, and M.Srinivasan. 1988. Respiratory cytopathology in chlorine gas toxicity: A study in 28 subjects. Diagn. Cytopathol. 4(1):28–32.

Silver, S.D., and F.P.McGrath. 1942. Chlorine: Median Lethal Concentration for Mice. Tech. Rep. 351. Edgewood Arsenal, MD: War Dept., Chemical Warfare Service. 14 pp. May 9.

Silver, S.D., F.P.McGrath, and R.L.Ferguson. 1942. Chlorine: Median Lethal Concentration for Mice. Tech. Rep. 373. Edgewood Arsenal, MD: War Dept., Chemical Warfare Service. 11 pp. July 17.

Skljanskaja, R.M., K.M.Klaus, and L.M.Ssidorowa. 1935. On the effect of chlorine on the female organism. [in German]. Arch. Hyg. Bakteriol. 114:103–114.

Stokinger, H.E. 1981. The halogens and the nonmetals boron and silicon. Pp. 2,937– 3,043 in Patty's Industrial Hygiene and Toxicology, 3rd Rev. Ed., Vol. 2B. Toxicology, G.D.Clayton and F.E.Clayton, eds. New York: John Wiley & Sons.

Takhirov, M.T. 1960a. Basic principles for the determination of allowable chlorine concentration in the atmosphere of inhabited localities. Pp. 31–49 in Limits of Allowable Concentrations of Atmospheric Pollutants, Book 4, V.A.Ryazanov, ed. Translated by B.S.Levine. Washington, DC: U.S. Public Health Service, January 1961. (Available from the National Technical Information Service, Springfield, VA, as publication no. TT-60–21475).

Takhirov, M.T. 1960b. Determination of limits of allowable concenraiton of chlorine in atmospheric air. Pp. 119–125 in U.S.S.R. Literature on Air Pollution and Related Occupational Diseases. A Survey, Vol. 3, B.S.Levine, ed. Washington, DC: U.S. Public Health Service. May 1960. (Available from the National Technical Information Service, Springfield, VA, as publication no. TT-60–21475).

Tatarelli, G. 1946. Cumulative chlorine poisoning on board a submarine. Ann. Naval. Colonial Med. 51(3):337–348. (Translated from Italian by Leo Kanner Associates for Information Services Division, U.S. Environmental Protection Agency, Redwood City, CA. March 1973).

Tawast, M., K.Linkama, and M.Siurala. 1956. Blood counts of industrial workers exposed to vaporized mercury and chlorine. Ann. Med. Int. Fenniae 45:59–61.

Underhill, F.P. 1920. The Lethal War Gases, Physiology and Experimental Treatment. New Haven: Yale University Press.

Vedder, E.B., and H.P.Sawyer. 1924. Chlorine as a therapeutic agent in certain respiratory diseases. JAMA 82:764–766.

Vernot, E.H., J.D.MacEwen, C.C.Haun, and E.R.Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2):417–423.

Weedon, F.R., A.Hartzell, and C.Setterstrom. 1940. Toxicity of ammonia, chlorine, hydrogen cyanide, hydrogen sulphide and sulphur dioxide gases. V. Animals. Contrib. Boyce Thompson Inst. 11:365–385.

Weill, H., R.George, M.Schwarz, and M.Ziskind. 1969. Late evaluation of pulmonary function after actue exposure to chlorine gas. Am. Rev. Respir. Dis. 99(3):374–379.

WHO (World Health Organization). 1982. Chlorine and Hydrogen Chlorine, Environmental Health Criteria 21. IPCS International Programme on Chemical Safety. Geneva: World Health Organization.

Winternitz, M.C., R.A.Lambert, L.Jackson, and G.H.Smith. 1920. The Pathology of Chlorine Poisoning. New Haven: Yale University School of Medicine.

Withers, R.M.J., and F.P.Lees. 1985. The assessment of major hazards: The lethal toxicity of chlorine. Part 1. Review of information on toxicity. J. Hazard. Mater. 12:231–282.

Withers, R.M.J., and F.P.Lees. 1987. The assessment of major hazards: The lethal toxicity of chlorine. J. Hazard. Mater. 15:301–342.

Wolf, D.C., K.T.Morgan, E.A.Gross, C.Barrow, O.R.Moss, R.A.James, and J.A. Popp. 1995. Two-year inhalation exposure of female and male B6C3F1 mice and F344 rats to chlorine gas induces lesions confined to the nose. Fundam. Appl. Toxicol. 24:111–131.

Zwart, A., and R.A.Woutersen. 1988. Acute inhalation toxicity of chlorine in rats and mice: Time-concentration-mortality relationships and effects on respiration. J. Hazard. Mater. 19:195–208.

5

Hydrogen Chloride

This chapter reviews physical and chemical properties, toxicokinetics, and toxicologic and epidemiologic data on hydrogen chloride. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to crew members aboard a disabled submarine from exposure to hydrogen chloride and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to hydrogen chloride.

BACKGROUND INFORMATION

Hydrogen chloride is a colorless, nonflammable gas with a pungent, suffocating odor (ACGIH 1991). It is very hygroscopic and produces fumes in moist air. The chemical and physical properties of hydrogen chloride are summarized in Table 5–1.

Hydrogen chloride is an important industrial chemical. The anhydrous form is used in making alkyl chlorides and vinyl chloride from olefins and acetylene, respectively, and in hydrochlorination, alkylation, and polymerization reactions (Sax and Lewis 1987). The hydrated form of hydrogen chloride is hydrochloric acid, which also is used in idustrial processes.

TABLE 5–1 Physical and Chemical Properties for Hydrogen Chloride

Characteristic	Value
Synonyms	Muriatic acid, hydrochloric acid
CAS number	7647–01–1
Chemical formula	HCl
Molecular weight	36.47
Physical state	Colorless, fuming gas
Relative density	1.268 at 25°C
Boiling point/flash point	–85°C/nonflammable
Melting point	–114.22°C
Solubility	67.3 g per 100 g water at 30°C
Conversion factors in air (25°C, 1 atm)	1 mg/m^3=0.67 ppm 1 ppm=1.49 mg/m^3
Odor threshold	1–5 ppm

Abbreviation: CAS, Chemical Abstract Service.
Source: AIHA (1998); HDSB (2001); NRC (2000).

Hydrogen chloride can be produced from thermodegradation of chlorinated polymers (e.g., polyvinyl chloride (PVC) and chlorinated acrylics) (Coleman and Thomas 1954). When chlorinated polymers are heated to 300–900°C in air, more than 99.9% of the chlorine atoms are released as hydrogen chloride; the remaining chlorine atoms are released as carbonyl chloride. No chlorine gas is formed. Hydrogen chloride has been detected in fires involving the combustion of chlorinated polymers, most commonly PVC (Dyer and Esch 1976; Gold et al. 1978; Jankovic et al. 1991). Of hydrogen chloride released from PVC in fires, more than 2% was adsorbed to soot particles, and only about 0.8% reached the alveoli (Stone et al. 1973 as cited in the NRC 2000).

TOXICOKINETIC CONSIDERATIONS

Data on the absorption, distribution, metabolism, and excretion of hydrogen chloride are sparse. There are reports of severe nonlactic metabolic acidosis developing rapidly after ingestion of hydrochloric acid (suggesting systemic absorption from the gastrointestinal tract), but this effect has not been reported after dermal exposure to concentrated hydrochloric acid or after inhalation of hydrogen chloride vapor or aerosol. No studies were found on upper respiratory

tract absorption of hydrogen chloride; however, it is known that two other water-soluble gases, hydrogen fluoride and formaldehyde, are readily taken up by the upper respiratory tract (Morgan and Monticello 1990). Extrapolating results from studies of those gases to hydrogen chloride is difficult because both of them have significant systemic toxicity. Liver and kidney effects have been observed in experimental animals exposed by inhalation to hydrogen chloride, which suggests that the gas is absorbed from the respiratory tract (EPA 1994). However, the effects also could be attributed to disturbance of acid-base metabolism or to decreased blood oxygen concentrations attendant to pulmonary damage. Chloride ions derived from hydrogen chloride absorbed in the upper respiratory tract should be distributed throughout the body (NRC 2000). Hydrogen chloride is not metabolized.

HUMAN TOXICITY DATA

Hydrogen chloride is a strong irritant that primarily affects the respiratory tract, resulting in coughing, pain, inflammation, edema, and desquamation (NRC 1987). Because it is soluble in water and reacts with the surface components of the upper respiratory tract, hydrogen chloride is usually retained there. At high concentrations, it is possible that the scrubbing capacity of the upper respiratory tract could be overwhelmed and penetration to the bronchioles and alveoli could occur. Other effects that can result from exposure to moderate or high concentrations include nasal lesions, pulmonary edema, retrosternal pain, and dyspnea (Ellenhorn 1997). Severe pulmonary injury can result in death. Because chloride ions are normal electrolytes in the body, prolonged exposures to low concentrations or brief exposures to high concentrations will not perturb the electrolyte homeostasis in the body enough to result in any systemic toxicity (NRC 2000). This section reviews the available human toxicity data on hydrogen chloride; some of which are summarized in Table 5–2. No epidemiology studies were found.

Experimental Studies

Stevens et al. (1992) exposed 5 men and 5 women (aged 18–25) to filtered air or to hydrogen chloride at 0.8 ppm (parts per million) or 1.8 ppm for 45 min.The 45-min exposure sessions consisted of a 15-min exercise period on a treadmill walking at 2 miles per hour at an elevation grade of 10%, followed by a 15-minute rest period and then by another 15-min exercise period. Subjects were asked to report any symptoms, such as upper respiratory effects (sore

TABLE 5-2 Human Toxicity Data, Inhalation Exposure to Hydrogen Chloride

Subject	Concentration (ppm)	Duration	Effect	Reference
10 asthmatics (5 men and 5 women, aged 18-25)	0.0, 0.8, or 1.8	45 min (15 min exercise, 15 min rest, 15 min exercise)	No treatment-related effects, including increase in severity of upper respiratory, lower respiratory, other symptoms; no significant differences between treated and control groups in pulmonary function tests (total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, forced vital capacity, maximal flow at 50% and 75% of expired vital capacity); no changes in nasal power data between treated and control groups.	Stevens et al. 1992
Workers	<5	NR	Apparently not harmful	Elkins 1959
Workers	≥ 5	NR	Immediately irritating	Elkins 1959
Workers	10-50	Several hours	Tolerable	Henderson and Haggard 1943
Workers	>10	NR	Highly irritating	Elkins 1959
Workers	35	NR	Throat irritation	Henderson and Haggard 1943
Workers	50-100	1 h	Barely tolerable	Henderson and Haggard 1943
Workers	1,000-2,000	NR	Known to be extremely dangerous even at short exposures	Henderson and Haggard 1943

Abbreviations: NR, not reported.

throat, nasal discharge), lower respiratory effects (cough, chest pain or burning, dyspnea, wheezing), and other effects (fatigue, headache, dizziness, unusual taste or smell). Pulmonary function measurements were performed, including total respiratory resistance, thoracic gas volume at functional residual capacity, forced expiratory volume, forced vital capacity, and maximal flow at 50% and 75% of expired vital capacity. Nasal work of breathing and oral ammonia concentrations also were measured. No adverse treatment-related effects were observed.

Accidental Exposures

Three male police officers (aged 36–45) were exposed to unknown concentrations of sodium hydroxide, silicon tetrachloride, and hydrogen chloride from a roadside chemical spill (Promisloff et al. 1990). The officers developed reactive airways dysfunction syndrome (RADS), a type of bronchospastic airway disease that occurs after a single exposure to high concentrations of an irritating vapor, fume, or smoke. Subsequently episodes of bronchospasmcan be triggered by inhalation exposure to any irritant substance. A 41-yr old male (nonsmoker) with a history of asthma developed RADS after cleaning a pool with a solution containing hydrogen chloride (concentration not reported) (Boulet 1988).

No reports were found that described accidental dermal exposure to hydrogen chloride in humans. Even after dermal exposure to concentrated hydrochloric acid resulting in significant burns, there have been no reported cases suggesting systemic absorption or systemic toxicity.

Occupational Studies

Stokinger (1981) reported that repeated occupational exposure to hydrogen chloride mist at a high but not quantified concentration resulted in bleeding of the gums and nose and ulceration of the mucous membranes. Dental erosion (but not an increase in dental caries) was reported in 555 workers exposed to acids in battery, pickling, plating, and galvanizing operations (Ten Bruggen Cate 1968). These workers were exposed to various mineral acids, including hydrogen chloride.

EXPERIMENTAL ANIMAL TOXICITY DATA

Numerous experimental animal studies have examined the toxicity of hydrogen chloride. They are summarized below; the experimental details are presented in Table 5–3.

Acute Exposure

Several laboratories examined lethality as a result of inhalation exposure to hydrogen chloride. Rat LC_{50} (the concentration that causes death in 50% of test animals) ranges from 31,000 to 41,000 ppm for a 5-min exposure (Darmer et al. 1974; Higgins et al. 1972). Rat LC_{50} values for a 30-min exposure are 4,700 ppm for hydrogen chloride vapor and 5,600 ppm for aerosol (Darmer et al. 1974). The LC_{50} for a 60-min exposure is 3,124 ppm (Wohlslagel et al. 1976). Guinea pigs exposed at 586 ppm for 3 min died (Malek and Alarie 1989), but no deaths were reported in guinea pigs exposed at 162 ppm for 30 min (Malek and Alarie 1989). Two of eight guinea pigs exposed at 1,040 or 1,380 ppm for 30 min died, but no deaths were reported in guinea pigs exposed at 320 or 680 ppm for 30 min (Burleigh-Flayer et al. 1985).

Nonlethal toxicity studies demonstrate that hydrogen chloride is a sensory and respiratory irritant. At relatively low concentrations and short exposure times, hydrogen chloride can cause changes to the upper respiratory tract. Rats exposed at 200–1,500 ppm for 30 min showed a decrease in respiratory rate and minute volume, and nasal pathology (Hartzell et al. 1985; Stavert et al. 1991). Respiratory tract irritation was observed in rats exposed at 1,800–4,500 ppm for 60 min (Wohlslagel et al. 1976) and at 11,800–57,000 for 5 minutes (Kaplan et al. 1986; Darmer et al. 1974).

Mice showed extreme respiratory irritation when exposed at 410–5400 ppm for 60 min, 560–2,500 ppm for 30 min, or 3,200–30,000 ppm for 5 min (Darmer et al. 1974; Doub 1933; Wohlslagel et al. 1976). Guinea pigs exposed at 107 ppm for 30 min showed only mild sensory irritation, but guinea pigs exposed at 140– 1,040 ppm for 30 min showed more severe sensory irritation or incapacitation (Burleigh-Flayer et al. 1985; Malek and Alarie 1989). Exposure at 190 ppm for 5 min did not cause adverse effects in a baboon, but exposure at 500 or 5,000 ppm for 30 min caused increased respiratory rate and minute volume (Kaplan et al. 1988). Baboons exposed at 16,600–17,300 ppm for 5 min showed pulmonary edema, pneumonia, and bacterial infections; the animals died weeks after the exposure (Kaplan et al. 1988).

Although some reports state that vapor is more toxic at a given concentration than is aerosol because of the lack of desiccating activity with aerosols, hydrogen chloride is so water reactive that the emergency exposure guidance level documentation (NRC 1987) states that published reports are assumed to deal with hydrogen chloride aerosol unless specifically stated otherwise. Because of the predicted cold and humid atmosphere in a disabled submarine, exposures would likely be to aerosol rather than vapor. In rats and mice, there was no significant difference in toxicity between vapor and aerosol exposure at various concentrations.

TABLE 5-3 Experimental Animal Toxicity Data, Exposure to Hydrogen Chloride

Species	Exposure Route	Exposure Concentration, ppm	Exposure Duration	Effects	Reference
ACUTE TOXICITY (LETHALITY)					
Rat	Inhalation	41,000 (vapor) 31,000 (aerosol)	5 min	LC_{50}	Darmer et al. 1974
Rat	Inhalation	4,700 (vapor) 5,600 (aerosol)	30 min	LC_{50}	Darmer et al. 1974
Rat	Inhalation	1,813	60 min	0 of 10 died	Wohlslagel et al. 1976
Rat	Inhalation	2,585	60 min	2 of 10 died	Wohlslagel et al. 1976
Rat	Inhalation	3,274	60 min	6 of 10 died	Wohlslagel at al. 1976
Rat	Inhalation	3,941	60 min	8 of 10 died	Wohlslagel at al. 1976
Rat	Inhalation	4,455	60 min	10 of 10 died	Wohlslagel at al. 1976
Rat	Inhalation	30,000	5 min	0 of 10 died	Higgins et al. 1972
Rat	Inhalation	32,000	5 min	1 of 10 died	Higgins et al. 1972
Rat	Inhalation	39,800	5 min	6 of 10 died	Higgins et al. 1972
Rat	Inhalation	45,200	5 min	7 of 10 died	Higgins et al. 1972
Rat	Inhalation	57,290	5 min	9 of 10 died	Higgins et al. 1972
Mouse	Inhalation	13,700 (vapor) 11,200 (aerosol)	5 min	LC_{50}	Darmer et al. 1974
Mouse	Inhalation	2,600 (vapor) 2,100 (aerosol)	30 min	LC_{50}	Darmer et al. 1974

	Mouse	Inhalation	557	60 min	2 of 10 died	Wohlslagel et al. 1976
	Mouse	Inhalation	985	60 min	3 of 10 died.	Wohlslagel et al. 1976
	Mouse	Inhalation	1,387	60 min	6 of 10 died	Wohlslagel et al. 1976
	Mouse	Inhalation	1,902	60 min	8 of 10 died	Wohlslagel et al. 1976
	Mouse	Inhalation	2,476	60 min	10 of 10 died	Wohlslagel et al. 1976
	Mouse	Inhalation	3,200	5 min	1 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	5,060	5 min	1 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	6,145	5 min	2 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	6,410	5 min	0 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	7,525	5 min	6 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	8,065	5 min	2 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	9,276	5 min	5 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	13,655	5 min	6 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	26,485	5 min	13 of 15 died	Higgins et al. 1972
	Mouse	Inhalation	30,000	5 min	13 of 15 died	Higgins et al. 1972
	Guinea pig	Inhalation	586	3 min	100% mortality	Malek and Alarie 1989
	Guinea pig	Inhalation	162	30 min	No deaths	Malek and Alarie 1989
	Guinea pig	Inhalation	320 680 1,040 1,380	30 min	0 of 8 died 0 of 8 died 2 of 8 died 3 of 8 died	Burleigh-Flayer et al. 1985

Species	Exposure Route	Exposure Concentration, ppm	Exposure Duration	Effects	Reference
ACUTE EXPOSURE (NONLETHAL TOXICITY)					
Rat	Inhalation	200-300	30 min	30% decrease in respiratory rate and minute volume.	Hartzell et al. 1985
		780-1,500		60% decrease in respiratory rate and minute volume.	
Rat	Inhalation "nose-breathing rats" and "mouth-breathing rats"	1,300	30 min	6% of nose-breathing rats died versus 46% of mouth-breathing rats; necrosis of the mucosa, submucosa, bone, submucosal gland in the nose-breathing rats; necrosis of the tracheal mucosa and submucosa of the mouth-breathing rats; dry and wet lung weights elevated in the mouth-breathing rats but not the nose-breathing rats.	Stavert et al. 1991
Rat	Inhalation	1,800-4,500	60 min	Eye and mucous membrane irritation, respiratory distress, corneal opacity, erythema of exposed skin.	Wohlslagel et al. 1976
	Inhalation	11,800-18,400	5 min	Severe irritation of the respiratory tract and eyes.	Kaplan et al. 1986
Rat	Inhalation	30,000-57,000	5 min	Extreme irritation to mucous	Darmer et al. 1974

				membranes and some irritation to exposed skin.	
Mouse	Inhalation	410-5,400	30 min	Extreme irritation of mucous membranes and some irritation of exposed skin.	Doub 1933
Mouse	Inhalation	560-2,500	60 min	Eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of exposed skin.	Wohlslagel et al. 1976
Mouse	Inhalation	3,200-30,000	5 min	Extreme irritation of mucous membranes and some irritation to exposed skin.	Darmer et al. 1974
Guinea pig	Inhalation	107	30 min	No incapacitation; animals able to run on a wheel but showed signs of mild sensory irritation.	Malek and Alarie 1989
Guinea pig	Inhalation	140	30 min	Animals unable to run on a wheel by 17 min into exposure.	Malek and Alarie 1989
Guinea pig	Inhalation	160	30 min	Animals unable to run a wheel by 1.3 min into exposure.	Malek and Alarie 1989
Guinea pig	Inhalation	320	30 min	Sensory irritation began at 6 min; lung irritation began at 20 min.	Burleigh-Flayer et al. 1985
Guinea pig	Inhalation	590	30 min	Incapacitated at 0.7 min into exposure; lacrimation, frothing at the mouth, coughing, cyanosis, death in about 3 min.	Malek and Alarie 1989

Species	Exposure Route	Exposure Concentration, ppm	Exposure Duration	Effects	Reference
Guinea pig	Inhalation	680	30 min	Sensory irritation at <1 min; lung irritation at 13 min; corneal opacities in 1 of 4 animals.	Burleigh-Flayer et al. 1985
Guinea pig	Inhalation	1,040	30 min	Sensory irritation at <1 min; lung irritation at 9 min; corneal opacities in 4 of 8 animals; squamous metaplasia with ciliary loss and submucosal inflammation in large airways and multifocal acute alveolitis 2 d after exposure; goblet-cell hyperplasia and mild inflammation in large airways, mild lymphoid hyperplasia and interstitial inflammation in the lung 15 d after exposure.	Burleigh-Flayer et al. 1985
Guinea pig	Inhalation	1,380	30 min	Sensory irritation at <1 min; lung irritation at 4 min; corneal opacities in 5 of 8 animals.	Burleigh-Flayer et al. 1985
Baboon (n = 1)	Inhalation	190	5 min	No sign of irritation.	Kaplan et al. 1988

Baboon (n = 3)	Inhalation	500	30 min	Increased respiratory rate and minute volume during exposure; no changes in lung function, arterial pH, pO_2, or pCO_2 at 3 d or 3 mo after exposure.	Kaplan et al. 1988
Baboon (n = 3)	Inhalation	810-940	5 min	Frothing at the mouth and coughing.	Kaplan et al. 1988
Baboon (n = 3)	Inhalation	5,000	30 min	Increased respiratory rate and minute volume during exposure; hypoxemia; normal chest X-ray 1 h after exposure; normal lung function 3 d or 3 mo after exposure.	Kaplan et al. 1988
Baboon (n = 2)	Inhalation	16,600-17,300	5 min	Head shaking, profuse salivation, blinking, eye rubbing during exposure; severe dyspnea after exposure; lung edema with tracheitis 18 or 76 d after exposure; died of pneumonia.	Kaplan et al. 1988
REPEATED EXPOSURE					
Rat	Inhalation	10	6 h/d, 5 d/wk for 90 d	Significant increase in incidence of minimal rhinitis in F344 rats, but not in Sprague-	Toxigenics 1983

Species	Exposure Route	Exposure Concentration, ppm	Exposure Duration	Effects	Reference
				Dawley rats; no changes in urinalysis, serum chemistry, hematology.	
Rat	Inhalation	10	6 h/d, 5 d/wk for 128 wk	Incidence of mucosal hyperplasia increased in the larynx and trachea, not in the nose. No increase in tumor incidence.	Sellakumar et al. 1985
Rat	Inhalation	20	6 h/d, 5 d/wk for 90 d	Mild rhinitis, but no histopathology in other tissues. No changes in urinalysis, serum chemistry, hematology.	Toxigenics 1983
Rat	Inhalation	50	6 h/d, 5 d/wk for 90 d	Depressed body weight gain in wk 3-8 exposure in males; minimal to mild rhinitis. No change in urinalysis, serum chemistry, hematology. No histopathology in tissues other than nose.	Toxigenics 1983
Mouse	Inhalation	10	6 h/d, 5 d/wk for 90 d	No significant changes in histopathology; no changes in urinalysis, serum chemistry, or hematology.	Toxigenics 1983

Mouse	Inhalation	20	6 h/d, 5 d/wk for 90 d	Minimal increase in eosinophilic globules in nose. No histopathology in other tissues; no changes in urinalysis, serum chemistry, hematology.	Toxicgenics 1983
Mouse	Inhalation	50	6 h/d, 5 d/wk for 90 d	Pigmented macrophages in lips; minimal ulcerative cheilitis; minimal to mild eosinophilic globules in nose. No changes in urinalysis, serum chemistry, hematology. No histopathology changes in tissues other than lip or nose. Depressed body weight gain.	Toxicogenics 1983
Mouse	Inhalation	310	6 h/d for 5 d	Necrosis, exfoliation, erosion, ulceration of respiratory epithelium in the nose. No lung injury.	Buckley et al. 1984
Guinea pig	Inhalation	34	6 h/d, 5 d/wk for 4 4wk	No histopathology	Machle et al. 1942
Guinea pig	Inhalation	67	6 h/d for 5 d	Mild bronchitis with some peribronchial fibrosis. No deaths.	Machle et al. 1942

Species	Exposure Route	Exposure Concentration, ppm	Exposure Duration	Effects	Reference
Guinea pig	Inhalation	100	6 h/d for 50 d	Signs of agitation; nasal discharge and mild lacrimation in the first hour of each day of exposure. No changes in red blood cell count, hemoglobin concentration, body-weight gain, bactericidal capacity of lungs, or susceptibility to pulmonary challenges with bacteria. Slight emphysema.	Ronzani 1909, as cited in NRC 2000

Abbreviations: LC_{50}, median lethal concentration; ppm, parts per million.

Repeated Exposure

Rats and mice exposed by inhalation at 10–50 ppm for 6 h/d, 5 d/wk for 90 d exhibited no significant histopathology, although the rats exposed at 50 ppm did show mild rhinitis (Toxigenics 1983). Mice exposed at 310 ppm for 6 h/d for 5 d showed necrosis, exfoliation, erosion, and ulceration of the respiratory epithelium in the nose (Buckley et al. 1984). No effects were observed in guinea pigs exposed at 34 ppm for 6 h/d, 5 d/wk for 4 wk (Machle et al. 1942). Respiratory effects were observed in guinea pigs exposed at 67 ppm for 6 h/d for 5 d and at 100 ppm for 6 h/d for 50 d (Machle et al. 1942; Ronzani 1909, as cited in NRC 2000).

NAVY'S RECOMMENDED SEALS

The Navy proposes to set a SEAL 1 of 2.5 ppm and a SEAL 2 of 25 ppm for exposure to hydrogen chloride. Those values appear to be based on the Short-Term Public Limits and the Public Emergency Limits (NRC 1987).

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Recommended exposure guidance levels for hydrogen chloride from other organizations are summarized in Table 5–4. The 24-h emergency exposure guidance level (EEGL) is the most relevant guidance level to compare to the SEALs (NRC 1987). EEGLs were developed for healthy military personnel for emergency situations. An important difference between EEGLs and SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for EEGLs. Therefore, the SEALs are higher than the corresponding EEGLs.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 2.5 ppm for hydrogen chloride is too conservative. The subcommittee

TABLE 5–4 Recommendations from Other Organizations for Hydrogen Chloride

Organization	Type of Exposure Level	Recommended Exposure Level	Reference
ACGIH	TLV-C	5 ppm	ACGIH 1998
AIHA	ERPG-1	3 ppm	AIHA 1998
	ERPG-2	20 ppm	
	ERPG-3	150 ppm	
DFG	MAK (8 h/d during a 40-h workweek)	5 ppm	DFG 1997
	Peak Limit (5 min maximum duration, 8 times per shift)	10 ppm	
NAC	Proposed AEGL-1	1.8 ppm	Federal Register, June 23, 2000, 65 (122):39263–39277.
	Proposed AEGL-2	2.7 ppm	
	Proposed AEGL-3	13 ppm	
NASA	SMAC:		NRC 2000
	1 h	5 ppm	
	24 h	2.5 ppm	
	7 d	1.0 ppm	
	30 d	1.0 ppm	
	180 d	1.0 ppm	
NIOSH	Ceiling Concentration	5 ppm	NIOSH 1990
NIOSH	IDLH	50 ppm	NIOSH 1997
NRC	90 d CEGL	0.5 ppm	NRC 1987
NRC	SPEGL:		NRC 1987
	1 h	1 ppm	
	24 h	1 ppm	
NRC	EEGL:		NRC 1987
	10 min	100 ppm	
	1 h	20 ppm	
	24 h	20 ppm	
OSHA	PEL-C	5 ppm	NIOSH 1990

Abbreviations: ACGIH, American Conference on Governmental Industrial Hygienists; AEGL, acute exposure guideline level; AIHA, American Industrial Hygiene Association; CEGL, continuous exposure guidance level; DFG, Deutsche Forschungsgemeinschaft; EEGL, emergency exposure guidance level; ERPG, emergency response planning guideline; IDLH, immediately dangerous to life and health; MAK, maximum concentration value in the workplace; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL-C, permissible exposure level—ceiling; ppm, parts per million; SMAC, spacecraft maximum allowable concentration; SPEGL, short-term public emergency guidance level; TLV-C, Threshold Limit Value-ceiling.

recommends a SEAL 1 of 20 ppm. No relevant human data are available on hydrogen chloride for deriving SEALs. The subcommittee's recommended SEAL 1 is based on a study in which the RD_{50} (50% decrease in respiratory rate) for hydrogen chloride was found to be 309 ppm in mice (Kane et al. 1979). Applying an uncertainty factor of 10 to account for interspecies differences, the SEAL 1 would be 31 ppm. Because of the paucity of human and animal data and the longer duration of exposure (up to 10 d), the subcommittee recommends a SEAL 1 of 20 ppm. At low concentrations (such as 20 ppm), the toxicity of hydrogen chloride depends on concentration, rather than dose (i.e., Haber's Rule is not applicable) (NRC 1987). The subcommittee concludes that healthy submariners should be able to tolerate irritative effects associated with exposures to less than 20 ppm for up to 10 d. The subcommittee's recommended SEAL 1 of 20 ppm is also supported by studies in which rats, mice, and guinea pigs were exposed to hydrogen chloride at 10–50 ppm for 6 h/d, 5 d/wk, for 90 d (rats and mice) or 28 d (guinea pigs) and no significant irritation or systemic effects were observed (Toxigenics 1983; Machle et al. 1942).

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 25 ppm for hydrogen chloride is too conservative. The subcommittee recommends a SEAL 2 of 35 ppm. The subcommittee's recommendation is based on a study in which a baboon exposed at a concentration of 190 ppm hydrogen chloride for 5 min showed no signs of irritation and baboons exposed at a concentration of 500 ppm for 30 min had only minor, transient respiratory effects (Kaplan et al. 1988). The recommended SEAL 2 is further supported by a study in which guinea pigs exposed to hydrogen chloride at a concentration of 107 ppm for 30 min showed only mild sensory irritation and no incapacitation (Malek and Alarie 1989). Since the toxicity of hydrogen chloride depends on concentration, rather than dose, and Haber's rule is not applicable to hydrogen chloride (NRC 1987), the subcommittee concludes that exposure of healthy submariners at 35 ppm for 24 h would produce moderate irritative effects that would be tolerable and would not produce irreversible health effects.

DATA GAPS AND RESEARCH NEEDS

The subcommittee recommends that the Navy consider conducting the following studies:

- Healthy volunteers—people with no asthma or other respiratory sensitivities—be studied to determine the actual NOAEL and LOAEL for hydrogen chloride;
- The absorption (if any) of hydrogen chloride vapor and aerosol through intact human skin in vitro should be studied;
- Additional information on the interaction of hydrogen chloride and the other irritant gases should be obtained;
- Finally, the potential effects of hyperbaric atmospheres under the conditions found in a disabled submarine should be studied as they obtain in the case of hydrogen chloride exposures.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Hydrogen chloride. Pp. 773–774 in Documentation of the Threshold Limit Values and Biological Exposure Indexes, Vol. II, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1998. Threshold Limit Values and Biological Exposure Indexes. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 1998. The AIHA Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Hydrogen chloride. Fairfax,VA: American Industrial Hygiene Association.

Boulet, L.P. 1988. Increases in airway responsiveness following acute exposure to respiratory irritants: reactive airway dysfunction syndrome or occupational asthma? Chest 94(3):476–481.

Buckley, L.A., X.Z.Jiang, R.A.James, K.T.Morgan, and C.S.Barrow. 1984. Respiratory tract lesions induced by sensory irritants at the RD_{50} concentration. Toxicol. Appl. Pharmacol. 74 (3):417–429.

Burleigh-Flayer, H., K.L.Wong, and Y.Alarie. 1985. Evaluation of the pulmonary effects of HCl using CO_2 challenges in guinea pigs. Fundam. Appl. Toxicol. 5(5): 978–985.

Coleman, E.H., and C.H.Thomas. 1954. The products of combustion of chlorinated plastics. J. Appl. Chem. 4:379–383.

Darmer, K.L., E.R.Kinkead, and L.C.DiPasquale. 1974. Acute toxicity in rats and mice exposed to hydrogen chloride gas and aerosols. Am. Ind. Hyg. Assoc. J. 35(10):623– 631.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, First Ed. Report No. 33. Weinheim: Wiley-VCH.

Doub, H.P. 1933. Pulmonary changes from inhalation of noxious gases. Radiology 21:105–113.

Dyer, R.F., and V.H.Esch. 1976. Polyvinyl chloride toxicity in fires. Hydrogen chloride toxicity in fire fighters. JAMA 235(4):393–397.

Ellenhorn, M.J. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, 2nd Ed. Baltimore: Williams and Wilkins.

Elkins, H.B. 1959. Hydrogen chloride. Pp. 79–80 in The Chemistry of Industrial Toxicology, 2nd Ed. New York: Wiley.

EPA (U.S. Environmental Protection Agency). 1994. Hydrogen chloride. Integrated Risk Information System. [Online]. Available: http://www.epa.gov/ngispgm3/iris/subst/0396.htm (Last updated: May 5, 1998).

Gold, A., W.A.Burgess, and E.V.Clougherty. 1978. Exposure of firefighters to toxic air contaminants. Am. Ind. Hyg. Assoc. J. 39(7):534–539.

Hartzell, G.E., H.W.Stacy, W.G.Swiztzer, D.N.Priest, and S.C.Packham. 1985. Modeling of toxicological effects of fire gases: 4. Intoxication of rats by carbon monoxide in the presence of an irritant. J. Fire Science. 3:263–279.

Henderson, Y., and H.W.Haggard. 1943. Hydrochloric acid (hydrogen chloride). Pp. 126–127 in Noxious Gases and the Principles of Respiration Influencing Their Action , 2nd Ed. New York: Reinhold.

Higgins, E.A., V.Fiorca, A.A.Thomas, and H.V.Davis. 1972. Acute toxicity of brief exposures to HF, HCL, NO2, and HCN with and without CO. Fire Tech. 8:120– 130.

HSDB (Hazardous Substances Data Bank). 2001. Hydrogen chloride. [Online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~BAA9AaqkJ:1. [April 19, 2001].

Jankovic, J., W.Jones, J.Burkhart, and G.Noonan. 1991. Environmental study of firefighters. Ann. Occup. Hyg. 35(6):581–602.

Kane, L.E., C.S.Barrow, and Y.Alarie. 1979. A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am. Ind. Hyg. Assoc. J. 40(3):207– 229.

Kaplan, H.L., A.F.Grand, W.G.Switzer, D.S.Mitchell, W.R.Rogers, and G.E.Hartzell. 1986. Effects of combustion gases on escape performance of the baboon and the rat. Danger Properties of Industrial Materials Report (July/Aug.):2–12.

Kaplan, H.L., A.Anzueto, W.G.Switzer, and R.K.Hinderer. 1988. Effects of hydrogen chloride on respiratory response and pulmonary function of the baboon. J. Toxicol. Environ. Health 23 (4):473–493.

Machle, W., K.V.Kitzmiller, E.W.Scott, and J.F.Treon. 1942. The effect of the inhalation of hydrogen chloride. J. Ind. Hyg. Toxicol. 24:222–225.

Malek, D.E., and Y.Alarie. 1989. Ergometer within a whole-body plethysmograph to evaluate performance of guinea pigs under toxic atmospheres. Toxicol. Appl. Pharmacol. 101 (2):340–355.

Morgan, K.T., and T.M.Monticello. 1990. Airflow, gas deposition, and lesion distribution in the nasal passages. Environ. Health Perspect. 85:209–218.

NIOSH (National Institute for Occupational Safety and Health). 1990. NIOSH pocket guide to chemical hazards. DHHS (NIOSH) Publ. No. 90–117. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publ. No. 97–140. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, OH.

NRC (National Research Council). 1987. Hydrogen Chloride. Pp. 17–30 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol.7. Washington, DC: National Academy Press.

NRC (National Research Council). 2000. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

Promisloff, R.A., G.S.Lenchner, A.Phan, and A.V.Cichelli. 1990. Reactive airway dysfunction syndrome in three police officers following a roadside chemical spill. Chest 98(4):928–929.

Ronzani, E. 1909. Concerning the influence of inhaling irritating industrial gases on the strength of the body's defenses against infectious disease. Arch. F. Hyg. 70:217–269.

Sax, N.I., and R.J.Lewis, Sr. 1987. Pp. 615 in Hawley's Condensed Chemical Dictionary, 11th Ed. New York: Van Nostrand Reinhold.

Sellakumar, A.R., C.A.Snyder, J.J.Solomon, and R.E.Albert. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81(3 Pt 1):401–406.

Stavert, D.M., D.C.Archuleta, M.J.Behr, and B.E.Lehnert. 1991. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide in nose- and pseudo- mouth-breathing rats. Fundam. Appl. Toxicol. 16(4):636–655.

Stevens, B., J.Q.Koenig, V.Rebolledo, Q.S.Hanley, and D.S.Covert. 1992. Respiratory effects from the inhalation of hydrogen chloride in young adult asthmatics. J. Occup. Med. 34(9):923–929.

Stokinger, H.E. 1981. The halogens and nonmetals boron and silicon. Pp. 2937–3043 in Patty's Industrial Hygiene and Toxicology, Vol. IIB. Toxicology, 3rd. Ed., G.D. Clayton, and F.E.Clayton, eds. New York: John Wiley & Son.

Stone, J.P., R.N.Hazlett, J.E.Johnson, and H.W.Carhart. 1973. The transport of hydrogen chloride by soot burning polyvinyl chloride. J. Fire Flam. 4:42–51.

ten Bruggen Cate, H.J. 1968. Dental erosion in industry. Br. J. Ind. Med. 25(4):249– 266.

Toxigenics. 1983. 90-Day Inhalation Toxicity Study of Hydrogen Chloride Gas in B6C3F1 Mice, Sprague-Dawley Rats, and Fischer-344 Rats. Rep. No. 420–1087. CIIT Docket No. 20915. Toxigenics, Decatur, IL.

Wohlslagel, J., L.C.DiPasquale, and E.H.Vernot. 1976. Toxicity of solid rocket motor exhaust: effects of HCl, HF, and alumina on rodents. J. Combust. Toxicol. 3:61–70.

6

Hydrogen Cyanide

This chapter reviews physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on hydrogen cyanide. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine from exposure to hydrogen cyanide and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 days). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to hydrogen cyanide.

BACKGROUND INFORMATION

Hydrogen cyanide is a colorless, poisonous liquid with a boiling point of 25.7° C (ATSDR 1997). Thus, at room temperature, hydrogen cyanide exists primarily as a gas. It has a faint odor of bitter almonds (ATSDR 1997), although not everyone is able to smell it (Hall and Rumack 1986). The chemical and physical properties of hydrogen cyanide are summarized in Table 6–1.

The major uses for hydrogen cyanide are in nylon and methyl methacrylate production (ATSDR 1997). It also is used in electroplating and mining and as an insecticide and rodenticide for fumigating enclosed spaces (e.g., ships and buildings) (ACGIH 1996; ATSDR 1997).

TABLE 6–1 Summary of Physical and Chemical Properties for Hydrogen Cyanide

Characteristic	Value
Molecular formula	HCN
Chemical structure	H—C`N
Molecular weight	27.03
CAS number	74–90–8
Synonyms	Formonitrile, hydrocyanic acid, prussic acid
Physical state	Gas or liquid
Color	Colorless gas or bluish-white liquid
Odor	Bitter almond odor
Odor threshold	0.58 ppm
	Low threshold, 0.9 ppm
	High threshold, 5.0 ppm
Melting point	13.4°C
Boiling point	25.70°C
Solubility in water	Miscible
Vapor pressure	630 mm Hg at 20°C
	807 mm Hg at 27°C
Vapor density (air=1)	0.941
Conversion factors	1 ppm=1.10 mg/m^3
25°C, 1 atm	1 mg/m^3=0.91 ppm

Abbreviations: CAS, Chemical Abstract Service.
Sources: Hartung 1994; Budavari et al. 1996; ATSDR 1997.

In 1993, an estimated total of 2.23 million pounds of hydrogen cyanide (approximately 73.1% of the total environmental release) was released into the air from U.S. industrial facilities (EPA 1995). Hydrogen cyanide also is released into the air from natural biogenic processes of plants, bacteria, and fungi; however, an estimate of that amount is not available (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; Fiksel et al. 1981; Knowles 1988). Biomass burning could represent a significant source (1.1–3.7 billion pounds annually) of atmospheric hydrogen cyanide (Crutzen and Carmichael 1993; Lobert and Warnatz 1993). Lowry et al. (1985) detected hydrogen cyanide in 12% of the fires they studied in Dallas, Texas. In 10% of the fires in which hydrogen cyanide was

detected, concentrations reached 15 ppm (parts per million). The maximum hydrogen cyanide concentration detected was 40 ppm.

Humans normally are exposed to cyanide from ingesting cyanide- and amygdalin-containing foods or foods that contain fumigation residues and from inhaling cigarette smoke, automobile exhaust, and smoke from fires (HSDB 2001; NIOSH 1976). Each puff from an unfiltered cigarette contains 35 μg (micrograms) of hydrogen cyanide and the lung is exposed to a concentration of approximately 46 ppm (Carson et al. 1981).

Trace amounts of cyanide are present normally in healthy people. The cyanide probably comes from the breakdown of cyanogenic food, from bacterial actions in the gastrointestinal tract, or from inhaled cigarette smoke (Ansell and Lewis 1970).

TOXICOKINETIC CONSIDERATIONS

This section provides information on absorption, distribution, metabolism, and excretion of hydrogen cyanide in humans and experimental animals exposed by inhalation or dermal contact.

Absorption

Inhalation

Hydrogen cyanide is a weak acid with a dissociation constant of 4.93×10^{-10} and pKa of 9.31 (Weast et al. 1985). It is miscible in water and absorbed by moist respiratory tissues. Hydrogen cyanide is moderately lipid soluble and can diffuse across cellular membranes and is absorbed by the lung (Wolfsie and Shaffer 1959). Landahl and Herrmann (1950) measured retention of hydrogen cyanide in the nose and lung of human subjects. Two subjects inhaled 450 milliliters (mL) of hydrogen cyanide at 0.46–4.6 ppm in 1.5 s and held their breath for 2 s. The lung retained 58.5% of the inhaled hydrogen cyanide; when holding time was increased to 4 s, retention increased to 73%. Nasal absorption was estimated at 10–20% (Landhal and Herrmann 1950). The authors concluded that approximately 75% of hydrogen cyanide inhaled during normal breathing would be retained in the body. Hydrogen cyanide uptake in monkeys exposed by inhalation (face masks were used) was rapid, and the blood cyanide concentration reached steady state in 10–20 min (Purser et al. 1984). Dogs exposed by inhalation to an unknown concentration of hydrogen cyanide absorbed 16.0 milligrams

(mg) (1.55 milligrams per kilogram (mg/kg)) and 10.1 mg (1.11 mg/kg). The dose was fatal, and the dogs died in 15 and 10 min, respectively.

Dermal

There is evidence that hydrogen cyanide gas can be absorbed through the skin. Three men protected by gas masks in an atmosphere containing 20,000 ppm hydrogen cyanide experienced marked dizziness, weakness, and throbbing pulse after 8–10 min (Drinker 1932). The symptoms lasted for several hours, but the men made a complete recovery. Walton and Witherspoon (1926) studied dermal absorption in guinea pigs and dogs exposed to hydrogen cyanide vapor. Exposing a small area of the shaved abdomen of guinea pigs for 30–60 min resulted in rapid respiration, twitching of muscles, convulsions, and death. Shaved and unshaved dogs were exposed whole-body, except for the head and neck, to hydrogen cyanide vapor (Walton and Witherspoon 1926). Toxicity was not observed in the dogs after exposure at 4,975 ppm for 180 min. Exposure at 13,400 ppm for 47 min resulted in death of the animals, thus, suggesting dermal absorption.

Distribution

Inhalation

After absorption, hydrogen cyanide is rapidly distributed by the blood throughout the body (ATSDR 1997). A man who died after inhalation exposure to hydrogen cyanide had 0.75 mg hydrogen cyanide/100 g of tissue in the lung, 0.42 mg/kg in the heart, 0.41 mg/kg in the blood, 0.33 mg/kg in the kidney, and 0.32 mg/kg in the brain (ATSDR 1997). Finck (1969) reported that tissue cyanide concentrations in a man who died from inhalation of hydrogen cyanide were 0.5 mg/100 mL in blood, 0.11 mg/100 g in the kidney, 0.07 mg/100 g in the brain, 0.03 mg/100 g in the liver, 0.2 mg/100 mL urine, and 0.03 mg/100 g in the gastric contents. Blood concentrations of cyanide in unexposed healthy adults average 0–10.7 μg/100 mL (mean 4.8 μg/100 mL) (Feldstein and Klendshoj 1954). Tissue distribution of cyanide at autopsy and whole-blood cyanide levels in humans fatally poisoned vary widely depending on the duration of survival, which, in turn, varies according to the delays to initial resuscitation, the administration of antidotal therapy, and the intensive care supportive measures applied (Hall et al. 1987).

Samples taken from rats exposed to fatal concentrations of hydrogen cyanide (356 or 1,180 ppm) showed that the pattern of tissue distribution of cyanide did not vary with the concentration used (Yamamoto et al. 1982). Data from the two dose groups were averaged. The tissue concentration of hydrogen cyanide was 4.4 μg/g wet weight in the lungs, 3.0 μg/g in the blood, 21.5 μg/g in the liver, 1.4 μg/g in the brain, and 0.68 μg/g in the spleen. Ballantyne (1983a) reported that rabbits exposed at 2,714 ppm for 5 minutes had cyanide concentrations of 170 μg/dL and 48 μg/dL in the blood and serum, 0 μg/100 g in the liver, 6 μg/100 g in the kidney, 50 μg/100 g in the brain, 62 μg/100 g in the heart, 54 μg/100 g in the lung, and 6 μg/100 g in the spleen. Hydrogen cyanide was identified in the lungs, blood, and heart of dogs exposed to unspecified fatal concentrations (Gettler and Baine 1938).

Dermal

No studies were found that examined distribution in humans after dermal exposure to hydrogen cyanide; there are limited data on the distribution in experimental animals after dermal exposure. Rabbits exposed by the dermal route to 33.75 mg CN^-/kg as hydrogen cyanide had cyanide concentrations of 310 μg/dL in the blood, 144 μg/dL in the serum, 26 μg/100 g in the liver, 66 μg/100 g in the kidney, 97 μg/100 g in the brain, 10 μg/100 g in the heart, 120 μg/100 g in the lungs, and 21 μg/100 g in the spleen (Ballantyne 1983a).

Metabolism

Hydrogen cyanide is metabolized through several pathways. In the major metabolic pathway (60–80% of absorbed cyanide), cyanide is converted to thiocyanate in a reaction that is catalyzed by rhodanase or 3-mercaptopyruvate sulfur transferase (Baumann et al. 1934; Himwich and Saunders 1948; Wood and Cooley 1956; Singh et al. 1989). Minor pathways include the oxidation of hydrogen cyanide or thiocyanate to carbon dioxide, reaction with cystine to form 2-aminothiazoline-4-carboxylic acid and 2-imnothizolidine-4-carboxylic acid, reaction with hydroxocobalamine to form cyanocobalamin, and conversion of hydrogen cyanide to formic acid, which enters one-carbon metabolism in the body (Wood and Cooley 1956; Boxer and Rickards 1952; Ansell and Lewis 1970; Baumeister et al. 1975).

Elimination

No studies were found that examined elimination in humans or experimental animals exposed to hydrogen cyanide by inhalation or dermal contact. Studies in rats exposed to cyanide orally or by subcutaneous injection showed that cyanide is excreted primarily as thiocyanate in the urine but also is exhaled as a gas and excreted in feces (Ansell and Lewis 1970; Leuschner et al. 1991; Okoh 1983).

HUMAN TOXICITY DATA

Hydrogen cyanide is extremely toxic to humans regardless of the route of exposure. Exposure to high concentrations of hydrogen cyanide can lead quickly to incapacitation and death. Hydrogen cyanide primarily acts by directly inhibiting cellular respiration by binding to cytochrome oxidase, a terminal enzyme in the mitochondrial electron transport chain. As tissue oxygen concentrations rise, there is increased tissue oxygen tension and a decreased unloading for oxyhemoglobin. Oxygen utilization in situ is blocked, slowing oxidative metabolism and reducing the ability to meet substrate needs. Thus, the primary targets are the tissues that are most sensitive to hypoxia—the brain and the heart. Typical symptoms of hydrogen cyanide poisoning include headache, vertigo, lack of motor coordination, nausea, vomiting, tachypnea, weak pulse, cardiac arrhythmia, and convulsion (NRC 2000). Respiratory rate and depth are initially increased (hyperpnea), but this is followed by rapid respiratory collapse and arrest. The cyanide encephalopathy lesions in the brain are attributed primarily to a histotoxic anoxia. For a detailed review of the mechanism of toxicity of hydrogen cyanide, see ATSDR's *Toxicological Profile for Cyanide* (ATSDR 1997).

This section reviews human toxicity data on hydrogen cyanide from experimental studies, accidental exposure, and occupational studies. The data are summarized in Table 6–2.

Experimental Studies

Because of the small margin of safety, few controlled experimental studies of hydrogen cyanide toxicity have been conducted with human subjects. Barcroft (1931) exposed a man at a nominal concentration of 625 ppm for 1.5 min in an airtight chamber. Five minutes after the start of the experiment, the man developed a "momentary feeling of nausea"; at 10 min, he had difficulty concentrating in a conversation. No toxic effects were observed in several human volunteers (number not reported) exposed at 240 or 360 ppm for 1.5–2 min (Grubbs 1917).

TABLE 6-2 Human Toxicity Data, Exposure to Hydrogen Cyanide

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
EXPERIMENTAL STUDIES					
1 man, 45 yr old, 70 kg	Inhalation	500-625	1.5 min	Nausea and difficulty in concentrating	Barcroft 1931
Several subjects	Inhalation	240	2 min	No symptoms	Grubbs 1917
Several subjects	Inhalation	360	1.5 min	No symptoms	Grubbs 1917
ACCIDENTAL EXPOSURES					
12 men	Inhalation	NR	NR	Dizziness, dyspnea, shaky feeling, headaches, nausea, unconsciousness	Peden et al. 1986
3 subjects	Inhalation	NR	NR	Semiconsciousness, headaches, nausea, sinus bradycardia, atrial fibrillation	Nagler et al. 1978
2 subjects' hands were exposed	Dermal	NR (liquid hydrogen cyanide)	NR	Breathing irregularities, coma, loss of deep reflexes, dilated pupils	Potter 1950
OCCUPATIONAL STUDIES					
36 workers, electroplating plant	Inhalation	6.4 ± 6.9 ppm 8.1 ± 8.2 ppm 10.4 ± 10.9 ppm	5-15 yr	Headaches, weakness, changes in taste and smell, nervous instability, throat irritation, lacrimation, vomiting, dyspnea, thyroid enlargement, increased rate of iodine accumulation in thyroid after 2 d of nonexposure.	El Ghawabi et al. 1975

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
Workers in electroplating plant	Inhalation	~5 ppm	NR	Nasal irritation, ulceration of the nasal septum.	Elkins 1959
23 male workers, electroplating plant	Inhalation	0.2-0.7 (Concentration measurement probably not accurate.)	NR	Workers complained of typical symptoms of hydrogen cyanide poisoning (not specified), no health effects reported, higher concentrations of blood and urine cyanide and thiocyanate were measured compared with controls.	Chandra et al. 1980
Workers, silver-reclaiming facility	Inhalation	15	NR	Loss of appetite, fatigue, dizziness, headaches, disturbed sleep, ringing in the ears, paresthesias of extremities, syncopes.	Blanc et al. 1985

Abbreviations: NR, not reported; ppm, parts per million.

Accidental Exposures

Some information about cyanide toxicity in humans is available from research on accidental exposures—for example in industrial accidents—although the usefulness of these data is limited because exposure durations and concentrations are often not known or not reported, because small numbers of individuals were exposed, and because other details, such as possible exposure to other chemicals, also are often not reported. Scrutiny of blood cyanide concentrations in victims of cyanide poisoning could be misleading for the purposes of characterizing dose-response relationships, depending on the length of the delay before performing the assay (Chaturvedi et al. 1995).

Fatalities have been reported after 30-min exposure to 135 ppm hydrogen cyanide and after 10 min exposure to 181 ppm (ATSDR 1997).

Workers accidentally exposed to unknown concentrations of hydrogen cyanide experienced central nervous system (CNS), respiratory, and cardiovascular effects (Peden et al. 1986; Nagler et al. 1978). Peden et al. (1986) reported that 12 men who were exposed to hydrogen cyanide in industrial accidents experienced dizziness (n=8), dyspnea (n=8), a shaky feeling (n=6), headaches (n= 4), nausea (n=4), and unconsciousness (n=5). Within approximately 10 min, the unconscious men regained consciousness. The men who reported suffering from headaches stated that the headaches persisted for up to 8 h after hospital admission. Nagler et al. (1978) reported 3 cases of hydrogen cyanide poisoning after the accidental addition of cyanide salt to a sulfuric acid bath in an electroplating factory in Belgium. The workers experienced semiconsciousness, headaches, nausea, sinus bradycardia, and atrial fibrillation.

Potter (1950) reported breathing irregularities, coma, loss of deep reflexes, and dilated pupils in 2 individuals whose hands were accidentally exposed to undetermined concentrations of hydrogen cyanide.

Wurzburg (1996) reported complete recovery among 36 workers with inhalation exposure to hydrogen cyanide who were treated with pressure oxygen resuscitation and/or the administration of amyl nitrate by inhalation. One-third of the workers were unconscious and one was convulsing at the time treatment was initiated.

Occupational Studies

Occupational exposures to cyanide resulting from unsafe work practices and inadequate worker protection procedures typically involve longer term exposure to lower concentrations than those that are identified in association with industrial accidents. El Ghawabi et al. (1975) reported on the effects of hydrogen

cyanide exposure in 36 chronically exposed (5–15 yr) workers in 3 electroplating factories in Egypt. The workers were all nonsmokers. Twelve 15-min breathing-zone air samples were collected in each factory. The average (standard deviation (SD), range) hydrogen cyanide concentrations in the three factories were reported to be 6.4 ppm (6.9, 4.2–8.8), 8.1 ppm (8.3, 5.9–9.6), and 10.3 ppm (10.9, 8.2–12.4), although the fact that the SDs are greater than the range of observed values makes these numbers of suspect validity. Compared with 20 unexposed control subjects of comparable age and social status, the workers reported significantly higher incidences of headache (81% of exposed individuals versus 30% of unexposed individuals), weakness (78% versus 20%), changes in taste and smell (78% versus 0%), giddiness (56% versus 15%), throat irritation (44% versus 5%), vomiting (44% versus 5%), effort dyspnea (44% versus 10%), lacrimation (25% versus 0%), and precordial pain (19% versus 5%). Fifty-six percent of workers had mild or moderate thyroid enlargement, although none showed evidence of clinical thyroid disease, and the likelihood of thyroid enlargement was not related to duration of employment at the plant. Uptake of ^{131}I by the thyroid was increased at 4 and 24 h, whereas ^{131}PBI concentrations at 72 h were within normal limits. This increased uptake was unexpected and could reflect an effect of acute cyanide withdrawal or the effect of a cyanide-induced iodine deficiency leading to an increased secretion of thyrotropic hormone. Compared with controls, workers had higher hemoglobin and lymphocyte counts, as well as a higher frequency of punctate basophilia (a sign associated with intoxication by chemicals other than cyanide). Urinary thiocyanate concentrations were correlated with the air sample concentrations.

Thirty-six workers in a silver-reclaiming facility were evaluated after one worker died from cyanide poisoning (Blanc et al. 1985). The mean duration of employment at the plant was 11 mo (SD 10 mo), and the workers were examined an average of 10 mo after their last employment at the plant. The day after the plant was closed, the time-weighted (24-h) average air concentration of cyanide was 15 ppm Retrospective reporting of symptoms experienced during the workers' period of employment revealed that 78% of them experienced headache, 72% dizziness, 68% nausea, 58% eye irritation, 58% loss of appetite, 47% epistaxis, 47% easy fatigue, 39% dyspnea, 31% chest pain, 25% hemoptysis, 14% paresthesias of extremities, and 14% syncope. The prevalence of these symptoms in the month preceding the interview ranged from 11% (nausea and chest pain) to 50% (eye irritation). Severity of symptoms was associated in a dose-response manner with an exposure index based on work history.

Two other studies examining workers in electroplating plants also reported respiratory symptoms and other unspecified "typical symptoms of hydrogen cyanide poisoning" (Chandra et al. 1980; Elkins 1959).

In general, the usefulness of the occupational studies in setting exposure limits is limited by methodology. In one study (Blanc et al. 1985), for instance,

a selection bias could have resulted from the fact that the subjects were identified by investigating officers of the state attorney general's office rather than through a complete ascertainment of all potentially exposed workers. In most studies, symptom prevalence was based on self-reports, and reports often were elicited by an interviewer who was not blinded to a worker's job history. Coexposure to other chemicals could have produced some of the nonspecific symptoms attributed to cyanide exposure. A high degree of uncertainty is associated with the concentrations of cyanide to which workers were exposed, and past exposures might have been higher than those measured by air sampling conducted after the identification of cyanide exposure as a problem in a plant. Exposure might have been oral or dermal, as well as by inhalation, resulting in overestimation of the toxicity of the measured air concentration. Furthermore, it might not be possible to generalize data from a setting that involves chronic, low-level hydrogen cyanide exposure to one of acute exposure to comparable air concentrations. Finally, the increased prevalence of symptoms in workers was detected only when investigators sought the data. The studies were not initiated in response to workers' complaints about poor health or about their inability to work well because of their symptoms.

EXPERIMENTAL ANIMAL TOXICITY DATA

There are numerous experimental animal studies examining hydrogen cyanide toxicity after acute exposure. The studies are summarized below, experimental details are presented in Table 6–3.

Acute Exposure

Several laboratories examined lethality due to inhalation exposure to hydrogen cyanide. The concentrations that cause death in 50% of test animals (LC_{50}) are similar across species. Rat LC_{50} values range from 196 to 503 ppm for exposures that last 5–15 minutes (Ballantyne 1983a; Barcroft 1931; Higgins et al. 1972; Vernot et al. 1977), from 110 to 200 ppm for 30-min exposures (Ballantyne 1983a; Kimmerle 1974; Levin et al. 1987), and from 120 to 144 ppm for 1 h exposures (Ballantyne 1983a; Kimmerle 1974). Mouse LC_{50} values ranged from 166 to 323 ppm for exposures up to 30 min (Higgins et al. 1972; Vernot et al. 1977; Matijak-Schaper and Alarie 1982). All Swiss-Webster mice exposed at 150 ppm for 4 h died, but only 1 of 10 mice exposed at 100 ppm for 4 h died (Pryor et al. 1975). Rabbit LC_{50} values range from 140 to 372 ppm for exposures up to 1 h (Ballantyne 1983a; Barcroft 1931). Etteldorf (1939) exposed dogs at 36 ppm for 10 min and 1 of the three animals died. One of 2 dogs died when exposed

TABLE 6–3 Experimental Animal Toxicity Data, Exposure to Hydrogen Cyanide

Species	Route	Concentration (ppm)	Duration	Effect	Reference
ACUTE EXPOSURE (LETHALITY)					
Rat	Inhalation	50	60 min	1 of 6 died	Barcroft 1931
Rat	Inhalation	68	6 h	3 of 10 died	Blank 1983
Rat	Inhalation	100	30 min	2 of 6 died	Barcroft 1931
			45 min	5 of 6 died	
			60 min	3 of 6 died	
Rat	Inhalation	110	1.5 h	All animals died	Dudley et al. 1942
Rat	Inhalation	120	1 h	LC_{50}	Kimmerle 1974
Rat	Inhalation	144	1 h	LC_{50}	Ballantyne 1983a
Rat	Inhalation	110	30 min	LC_{50}	Levin et al. 1987
Rat	Inhalation	157	30 min	LC_{50}	Ballantyne 1983a
Rat	Inhalation	200	30 min	LC_{50}	Kimmerle 1974
Rat	Inhalation	200	15 min	1 of 4 died	Barcroft 1931
			30 min	6 of 6 died	
Rat	Inhalation	240	6–12 min	3 of 4 died	Grubbs 1917
Rat	Inhalation	449	5 min	LC_{50}	Ballantyne 1983a
Rat	Inhalation	484	5 min	LC_{50}	Vernot et al. 1977
Rat	Inhalation	500	3 min	3 of 6 died	Barcroft 1931
			10 min	6 of 6 died	

Rat	Inhalation	503	5 min	LC_{50}	Higgins et al. 1972
Rat	Inhalation	1,339	1 min	LC_{50}	Ballantyne 1983a
Rat	Inhalation	3,438	10 sec	LC_{50}	Ballantyne 1983a
Mouse	Inhalation	100	12 hr	All animals died	Pryor et al. 1975
			4 hr	1 of 10 died	
Mouse	Inhalation	150	4 hr	All animals died	Pryor et a. 1975
Mouse	Inhalation	166	30 min	LC_{50}	Matijak-Schaper and Alarie 1982
Mouse	Inhalation	323	5 min	LC_{50}	Higgins et al. 1972; Vernot et al. 1977
Rabbit	Inhalation	100	60 min	2 of 2 survived	Barcroft 1931
Rabbit	Inhalation	140	60 min	2 of 4 died	Barcroft 1931
Rabbit	Inhalation	189	35 min	LC_{50}	Ballantyne 1983a
Rabbit	Inhalation	200	15 min	3 of 7 died	Barcroft 1931
Rabbit	Inhalation	300	10 min	2 of 4 died	Barcroft 1931
Rabbit	Inhalation	372	5 min	LC_{50}	Ballantyne 1983a
Rabbit	Inhalation	500	3 min	3 of 4 died	Barcroft 1931
			10 min	4 of 4 died	
Rabbit	Inhalation	2,213	45 s	LC_{50}	Ballantyne 1983a
Rabbit	Dermal	6.7 mg CN^-/kg as hydrogen cyanide	1 application	LD_{50}	Ballantyne 1983a

Species	Route	Concentration (ppm)	Duration	Effect	Reference
Rabbit	Ocular	1.0 mg CN^-/kg as hydrogen cyanide	1 application	LD_{50}	Ballantyne 1983b
Guinea pig	Dermal	Not stated		Death	Walton and Witherspoon 1926
Dog	Inhalation	36	10 min	1 of 3 died	Etteldorf 1939
Dog	Inhalation	60	1 h	4 of 4 survived	Barcroft 1931
Dog	Inhalation	70	30 min	2 of 2 survived	Barcroft 1931
Dog	Inhalation	100	15 min	1 of 2 died	Barcroft 1931
			30 min	2 of 2 died	
Dog	Inhalation	200	5 min	3 of 3 survived	Barcroft 1931
			10 min	1 of 3 died	
Monkey	Inhalation	100	60 min	8 of 8 survived	Barcroft 1931
Monkey	Inhalation	140	30 min	1 of 3 died	Barcroft 1931
Monkey	Inhalation	170	60 min	3 of 3 died	Barcroft 1931
Monkey	Inhalation	200	30 min	1 of 3 died	Barcroft 1931
Monkey	Inhalation	400	3 min	3 of 3 died	Barcroft 1931
Goat	Inhalation	140	60 min	8 of 8 survived	Barcroft 1931
Goat	Inhalation	200	30 min	3 of 4 died	Barcroft 1931
			60 min	4 of 8 died	

Goat	Inhalation	300	15 min	1 of 4 died	Barcroft 1931
Goat	Inhalation	400	10 min	3 of 4 died	Barcroft 1931
ACUTE EXPOSUE (NONLETHAL TOXICITY)					
Rat	Inhalation	50	3 min	1 paralyzed at 2.5 min; the other not paralyzed.	Moss et al. 1951
Rat	Inhalation	55	30 min	Changes in lung dynamics, lung phospholipids.	Bhattacharya et al. 1994
Mouse	Inhalation	23	30 min	Respiratory depression of 20%	Matijak-Schaper and Alarie 1982
Mouse	Inhalation	30	24 h	Lung congestion	Pryor et al. 1975
Mouse	Inhalation	41.7	30 min	Incapacitation	Sakurai 1989
Mouse	Inhalation	63	30 min	Respiratory depression of 50%	Matijak-Schaper and Alarie 1982
Mouse	Inhalation	120	30 min	Respiratory depression of 80%	Matijak-Schaper and Alarie 1982
Rabbit	Ocular	0.9 mg CN^-/kg as hydrogen cyanide	1 application	Keratitis, rapid breathing, weak and ataxic movements, convulsions, coma.	Ballantyne 1983b
Rabbit	Dermal	1.92 mg CN^-/kg as hydrogen cyanide	1 application	Tremors, retrocolic spasms, convulsions	Ballantyne 1994

Species	Route	Concentration (ppm)	Duration	Effect	Reference
Monkey	Inhalation	100–156	8–19min	Incapacitation	Purser et al. 1984
Monkey	Inhalation	60	30 min	Slight central nervous system effects	Purser et al. 1984
REPEATED EXPOSURE					
Rat	Inhalation	200	12.5 min every 4 d for a total of 5 exposures	Possible changes in blood enzymes attributed to cardiac effects.	O'Flaherty and Thomas 1982

Abbreviations: LC_{50}, median lethal concentration; LD_{50}, median lethal dose; ppm, parts per million.

at 100 ppm for 15 min and 1 of 3 dogs died when exposed at 200 ppm for 10 min (Barcroft 1931). No deaths occurred in dogs exposed at 60, 70, 100, or 200 ppm for 1 h, 30 min, 30 min, or 5 min, respectively (Barcroft 1931). Deaths occurred in goats exposed at 200–400 ppm for 10–60 min, but did not occur in goats exposed at 140 ppm for 60 min (Barcroft 1931). Monkeys exposed at 100 ppm for 1 h did not die (Barcroft 1931). One of 3 monkeys died when exposed at 140 ppm for 30 min; the same results were observed when monkeys were exposed at 200 ppm for 30 min (Barcroft 1931). All monkeys (3 in each group) died when exposed at 170 ppm for 60 min or 400 ppm for 3 min (Barcroft 1931).

The CNS, respiratory system, and possibly, the cardiovascular system of experimental animals are affected by exposure to hydrogen cyanide. Four cynomolgus monkeys exposed at 60 ppm for 30 min experienced a slight depressive effect on the CNS as shown by changes in brain wave activity and reduced auditory cortical evoked potential (Purser et al. 1984). Purser et al. (1984) found a roughly linear relationship between air concentration and time to incapacitation for 30-min exposures of 80–180 ppm (e.g., the regression suggested that increasing the concentration from 100 to 200 ppm reduced the time to incapacitation from 25 min to 2 min). Observed effects included hyperventilation (within 30 s), loss of consciousness, bradycardia with arrhythmias, and T-wave abnormalities. The animals recovered rapidly after exposure. Bhattacharya et al. (1994) exposed Wistar rats at 55 ppm for 30 min and found changes in the rats' lung parameters, including increases in air flow, transthoracic pressure, and tidal volume, as well as decreases in respiratory rate (60–70%) and minute volume. There was also a significant decrease in phospholipids in the lungs. Matijak-Schaper and Alarie (1982) reported that exposure of Swiss-Webster mice at 63 ppm for 30 min resulted in a 50% decrease in respiration rate. The incapacitation time for Jcl ICR mice exposed at 41.7 ppm was 30 min (Sakurai 1989).

Some studies suggest a synergistic lethality of cyanide and carbon monoxide, although data from other studies are more consistent with additivity. In white rats, Moss et al. (1951) reported that the LC_{50} was considerably reduced if exposure to hydrogen cyanide occurred in the presence of 2,000 ppm carbon monoxide (although hydrogen cyanide concentrations were calculated rather than measured directly in the exposure chamber). Similarly, Norris et al. (1986) found that the LC_{50} for potassium cyanide, administered intraperitoneally (4–9 mg/kg) was significantly lower in mice administered carbon monoxide (0.63–0.66%) than it was in mice pretreated with air. The data suggested a synergistic rather than an additive effect, although the mechanism was unclear insofar as carbon monoxide pretreatment did not alter blood cyanide concentrations. Chaturvedi et al. (1995) also found that co-exposure to carbon monoxide and hydrogen cyandide did not appreciably affect hydrogen cyanide uptake. In a set of experiments with Fischer-

344 male rats, however, Levin et al. (1987) reported that carbon monoxide and hydrogen cyanide acted additively rather than synergistically, which failed to support the conclusions of Moss et al. (1951). In fact, the results indicated that hydrogen cyanide exerts a depressive effect on carbon monoxide uptake. Other experiments in mice by Sakurai (1989) also failed to demonstrate a synergism between hydrogen cyanide and carbon monoxide exposures. Levin et al. (1987) did report, however, that the LC_{50} of hydrogen cyanide was reduced in the presence of 5% carbon dioxide.

Dermal

Dermal and ocular toxicity has been assessed in rabbits (Ballantyne 1983a,b). The LD_{50} (dose that is lethal to 50% of test animals) for dermal toxicity is 6.7 mg CN^-/kg as hydrogen cyanide; the LD_{50} for ocular toxicity is 1.0 mg CN^-/kg as hydrogen cyanide (Ballantyne 1983a,b). The effects observed when rabbits were exposed dermally at 1.92 mg CN^-/kg as hydrogen cyanide include tremors, retrocolic spasms, and convulsions. Rabbits that were administered 0.9 mg CN^-/ kg as hydrogen cyanide in their conjunctival sacs were reported to have keratitis, rapid breathing, weak and ataxic movements, convulsions, and coma (Ballantyne 1983a,b).

Repeated Exposure

O'Flaherty and Thomas (1982) subjected rats to 5 repeated exposures at 200 ppm for 12.5 min every 4 d. The animals showed increased cardiac-specific creatine phosphokinase in the blood and ectopic heartbeat during the first 2 min after injection of norepinephrine (after the fifth exposure). Cardiac lesions were not induced.

NAVY'S RECOMMENDED SEALS

The Navy proposes to set a SEAL 1 of 1 ppm and a SEAL 2 of 4.5 ppm for exposure to hydrogen cyanide. The Navy based the SEALs on NIOSH (1994) recommended daily limit of 4.7 ppm and on the American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV) (ACGIH 1998) of 4.5 ppm.

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Recommended exposure guidance levels for hydrogen cyanide from the NRC and other organizations are summarized in Table 6–4.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 1 ppm for hydrogen cyanide is too conservative. The subcommittee recommends a SEAL 1 of 10 ppm. This value is based on a study in which workers in an electroplating plant chemically exposed at 10 ppm for 5–15 years reported headaches, weakness, changes in taste and smell, nervous instability, throat irritation, lacrimation, vomiting, dyspnea, and thyroid enlargement (El Ghawabi et al. 1975). The subcommittee's recommended SEAL 1 is supported by an additional occupational study in which workers at a silver-reclaiming facility chemically exposed to hydrogen cyanide at a concentration of 15 ppm reported loss of appetite, fatigue, dizziness, headaches, disturbed sleep, ringing in the ears, paresthesia of extremities, and syncope. The subcommittee concludes that irritant effects associated with exposure to hydrogen cyanide at less than 10 ppm should be tolerable for up to 10 d.

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 4.5 ppm for hydrogen cyanide is too conservative. The subcommittee recommends a SEAL 2 of 15 ppm. The recommended SEAL 2 is also based on the El Ghawabi et al. (1975) study, which is discussed under the derivation of SEAL 1. It is supported by studies in monkeys that show some central nervous system effects (e.g., changes in brain wave activity and reduced auditory cortical evoked potential) occur after a 30-min exposure at a concentration of 60 ppm (Purser et al. 1984). The subcommittee concludes that exposures of submariners to hydrogen cyanide at a concentration of 15 ppm for only 1 d is not likely to produce any irreversible health effects.

TABLE 6–4 Recommendations from Other Organizations for Hydrogen Cyanide

Organization	Type of Exposure Level	Recommended Exposure Level	Reference
ACGIH	TLV-C	4.7 ppm (as cyanide)	ACGIH 1998
AIHA	ERPG1	NR	AIHA 2001
	ERPG2	10 ppm	
	ERPG3	25 ppm	
DFG	MAK (8 h/d during 40-h workweek)	10 ppm	DFG 1997
	Peak Limit (30 min maximum duration, 4 times per shift)	20 ppm	
NAC	Proposed AEGL-1	1.0 ppm	Federal Register, March 15, 2000, 65(51):14185–14197.
	Proposed AEGL-2	2.5 ppm	
	Proposed AEGL-3	6.6 ppm	
NASA	SMAC:		NRC 2000
	1 h	8 ppm	
	24 h	4 ppm	
	7 d	1 ppm	
	30 d	1 ppm	
	180 d	1 ppm	
NIOSH	Ceiling Concentration	4.7 ppm	NIOSH 1994
NIOSH	IDLH	50 ppm	NIOSH 1994; Ludwig et al. 1994
OSHA	PEL	10 ppm	NIOSH 1994

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; AIHA, American Industrial Health Association; DFG, Deutsche Forschungsgemeinschaft; ERPG, emergency response planning guideline; IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; NAC, National Advisory Committee; NASA, National Air and Space Administration; NIOSH, National Institute for Occupational Safety and Health; NR, not recommended; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure level; ppm, parts per million; SMAC, spacecraft maximum allowable concentrations; TLV-C, Threshold Limit Value-ceiling.

DATA GAPS AND RESEARCH NEEDS

As noted by NRC (2000), the major impediment to setting exposure limits for hydrogen cyanide is the absence of strong dose-response inhalation data for humans and animals, especially for lower exposure concentrations (less than 15 ppm) sustained over a period of days. Therefore, the subcommittee recommends that research be done to obtain dose-response data at concentrations of 5–15 ppm for exposures lasting up to 1 d. Additional data are also needed on the effects of combined exposure to hydrogen cyanide and other combustion gases. Determining whether the combined effects of exposure to carbon monoxide and hydrogen cyanide are additive or synergistic is an issue of particular importance, and therefore, research should be done to obtain that data. The impacts of other environmental parameters (e.g., humidity, temperature, pressure) of the disabled submarine environment on hydrogen cyanide toxicity also require additional study.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1996. Hydrogen cyanide and cyanide salts. Supplements to the Sixth Edition Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1998. Hydrogen Cyanide. Supplements to the Sixth Edition Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Ansell, M., and F.A.S.Lewis. 1970. A review of cyanide concentrations found in human organs. A survey of literature concerning cyanide metabolism, normal, non-fatal, and fatal body cyanide levels. J. Forensic Med. 17(4):148–155.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Cyanide (Update). U.S. Department for Health and Human Services. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Ballantyne, B. 1983a. The influence of exposure route and species on the acute lethal toxicity and tissue concentrations of cyanide. Pp. 583–586 in Developments in the Science and Practice of Toxicology, A.W.Hayes, R.C.Schnell, and T.S.Miya, eds. New York, NY: Elsevier.

Ballantyne, B. 1983b. Acute systemic toxicity of cyanides by topical application to the eye. J. Toxicol. Cutan. Ocul. Toxicol. 2:119–129.

Ballantyne, B. 1994. Acute percutaneous systemic toxicity of cyanides. Cutaneous Ocul. Toxicol. 13 (3):249–262.

Barcroft, J. 1931. The toxicity of atmospheres containing hydrocyanic acid gas. J. Hyg. 31(1):1–34

Baumann, E.J., D.B.Sprinson, and N.Metzger. 1934. The estimation of thiocyanate in urine. J. Biol. Chem. 105:269–277.

Baumeister, R.G., H.Schievelbein, and G.Zickgraf-Rudel. 1975. Toxicological and clinical aspects of cyanide metabolism. Arzneimittelforschung. 25(7):1056–1064.

Bhattacharya, R., P.Kumar, and A.S.Sachan. 1994. Cyanide induced changes in dynamic pulmonary mechanics in rats. Indian J. Physiol. Pharmacol. 38(4):281–284.

Blanc, P., M.Hogan, M.Mallin, D.Hryhorczuk, S.Hessl, and B.Bernard. 1985. Cyanide intoxication among silver-reclaiming workers . JAMA 253(3):367–371.

Blank, T.L. 1983. Inhalation Pilot Study of Hydrogen Cyanide Exposure in Sprague-Dawley Rats. Report No. MSL-2985. EPA OTS Submission 88–920007543. Monsanto Company.

Boxer, G.E., and J.C.Rickards. 1952. Studies on the metabolism of the carbon of cyanide and thiocyanate. Arch. Biochem. 39:7–26.

Budavari, S., M.J.O'Neil, A.Smith, P.E.Heckelman, and J.F.Kinneary, eds. 1996. The Merck Index, 12th Ed. Rahway, NJ: Merck.

Carson, B.L., H.V.Ellis, B.L.Herndon, E.M.Horn, and L.H.Baker. 1981. Hydrogen Cyanide Health Effects. EPA-460/3–81–026. Office of Mobile Source Air Pollution Control, U.S. Environmental Protection Agency, Ann Arbor, MI.

Chandra, H., B.N.Gupta, S.K.Bhargava, S.H.Clerk, and P.N.Mahendra. 1980. Chronic cyanide exposure: A biochemical and industrial hygiene study. J. Anal. Toxicol. 4(4):161–165.

Chaturvedi, A.K., D.C.Sanders, B.R.Endecott, and R.M.Ritter. 1995. Exposures to carbon monoxide, hydrogen cyanide and their mixtures: Interrelationship between gas exposure concentration, time to incapacitation, carboxyhemoglobin and blood cyanide in rats. J. Appl. Toxicol. 15(5):357–363.

Cicerone, R.J., and R.Zellner. 1983. The atmospheric chemistry of hydrogen cyanide (HCN). J. Geophys. Res. 88(C15):10689–10696.

Crutzen, P.J., and G.R.Carmichael. 1993. Modeling the influence of fires on atmospheric chemistry. Pp. 89–105 in Fire in the Environment: The Ecological, Atmospheric, and Climatic Importance of Vegetation Fires, P.J.Crutzen, and J.G. Goldammer, eds. New York: John Wiley& Sons.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, First Ed. Report No. 33. Weinheim: Wiley-VCH.

Drinker, P. 1932. Hydrocyanic acid gas poisoning by absorption through the skin. J. Ind. Hyg. 14 (1):1–2.

Dudley, H.C., T.R.Sweeney, and J.W.Miller. 1942. Toxicology of acrylonitrile (vinyl cyanide). J. Ind. Hyg. Toxicol. 24(1):255–258.

El Ghawabi, S.H., M.A.Gaafar, A.A.El-Saharti, S.H.Ahmed, K.K.Malash and R.Fares. 1975. Chronic cyanide exposure: A clinical, radioisotope, and laboratory study. Br. J. Ind. Med. 32(3):215–219.

Elkins, H.B. 1959. Pp. 51 in Chemistry of Industrial Toxicology, 2nd Ed. New York: Wiley.

EPA (U.S. Environmental Protection Agency). 1995. EPA Chemical Release Inventory (TRI). Bethesda, MD: National Library of Medicine.

Etteldorf, J.N. 1939. The treatment of gaseous hydrocyanic acid poisoning by sodium thiosulfate and sodium nitrite combination. J. Pharmacol. Exp. Ther. 66:125–131.

Feldstein, M., and N.C.Klendshoj. 1954. The determination of cyanide in biologic fluids by microdiffusion analysis. J. Lab. Clin. Med. 44(July):166–170.

Finck, P.A. 1969. Postmortem distribution studies of cyanide. Report of three cases. Med. Ann. Dist. Columbia 38(7):357–358.

Fiksel, J., C.Cooper, A.Eschenroeder, M.Goyer, J.Perwak, K.Scow, R.Thomas, W. Tucker, M.Wood, and M.W.Slimak. 1981. Exposure and Risk Assessment for Cyanide. EPA-440/4–85–008. NTIS PB85–220572. Office of Water Regulation and Standards, Office of Water and Waste Management, U.S. Environmental Protection Agency, Washington, DC.

Gettler, A.O., and J.O.Baine. 1938. The toxicology of cyanide. Am. J. Med. Sci. 195(2):182–198.

Grubbs, S.B. 1917. Detection of hydrocyanic acid gas. Use of small animals for this purpose. Pub. Health Rep. 32:565–570.

Hall, A.H., and B.H.Rumack 1986. Clinical toxicology of cyanide. Ann. Emerg. Med. 15(9):1067–1074.

Hall, A.H., B.H.Rumack, M.E.Schafer, and C.H.Linden. 1987. Clinical toxicology of cyanide: North American clinical experience. Pp. 312–333 in Clinical Toxicology of Cyanide, B.Ballantyne, and T.C.Marrs, eds. Bristol: Wright.

Hartung, R. 1994. Cyanides and nitriles. Pp. 3119–3172 in Patty's Industrial Hygiene and Toxicology, 4th Ed., Vol II, Part D. Toxicology, G.D.Clayton, and F.E.Clayton, eds. New York: John Wiley & Sons.

Higgins, E.A., V.Fiorca, A.A.Thomas and H.V.Davis. 1972. Acute toxicity of brief exposures to HF, HCI, NO2 and HCN with and without CO. Fire Technol. 8:120– 130.

Himwich, W.A., and J.P.Saunders. 1948. Enzymatic conversion of cyanide to thiocyanate. Am. J. Physiol. 153(May):348–354.

HSDB (Hazardous Substances Data Bank). 2001. Hydrogen cyanide. [Online]. Available http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAKVayr4:1 [May 9, 2001].

Kimmerle, G. 1974. Aspects and methodology for the evaluation of toxicological parameters during fire exposure. J. Fire Flammability/Combust. Toxicol. (Suppl.1):4– 51.

Knowles, C.J. 1988. Cyanide utilization and degradation by microorganisms. Pp. 3–15 in Cyanide Compounds in Biology, CIBA Foundation Symposium 140. Chichester: Wiley.

Landahl, H.D., and R.G.Herrmann. 1950. Retention of vapors and gases in the human nose and lung. Arch. Ind. Hyg. Occup. Med. 1:36–45.

Leuschner, J., A.Winkler, and F.Leuschner. 1991. Toxicokinetic aspects of chronic cyanide exposure in the rat. Toxicol. Lett. 57(2):195–201.

Levin, B.C., M.Paabo, J.L.Gurman, and S.E.Harris. 1987. Effects of exposure to single or multiple combinations of the predominant toxic gases and low oxygen atmospheres produced in fires. Fundam. Appl. Toxicol. 9(2):236–250.

Lobert, J.M., and J.Warnatz. 1993. Emission from the combustion process in vegetation. Pp. 15–37 in Fire in the Environment: The Ecological, Atmospheric, and Climatic Importance of Vegetation Fires, P.J.Crutzen, and J.G.Goldammer, eds. New York: John Wiley & Sons.

Lowry, W.T., L.Juarez, C.S.Petty, and B.Roberts. 1985. Studies of toxic gas production during actual structural fires in the Dallas area. J. Forensic Sci. 30(1):59–72.

Ludwig, H.R., S.G.Cairell, and J.J.Whalen. 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHS). Cincinnati, OH: National Institute for Occupational Safety and Health . PB94–195047, National Technical Information Service, Springfield, VA.

Matijak-Schaper, M., and Y.Alarie. 1982. Toxicity of carbon monoxide, hydrogen cyanide and low oxygen. Combust. Technol. 9:21–61.

Moss, R.H., C.F.Jackson, and J.Seiberlich. 1951. Toxicity of carbon monoxide and hydrogen cyanide gas mixtures. Arch. Ind. Hyg. Occup. Med. 4:53–64.

Nagler, J., R.A.Provoost and G.Parizel. 1978. Hydrogen cyanide poisoning: Treatment with cobalt EDTA. J. Occup. Med. 20(6):414–416.

NIOSH (National Institute for Occupational Safety and Health). 1976. Pp. 37–114 in Criteria for a Recommended Standard. Occupational Exposure to Hydrogen Cyanide and Cyanide Salts (NaCN, KCN, and Ca (CN)2). DHEW (NIOSH) Pub. No. 77–108. PB-266 230. U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, Washington, DC.

NIOSH (National Institute for Occupational Safety and Health). 1994. NIOSH Pocket Guide to Chemical Hazards. Publication 94–116. U.S. Department of Health and Human Services, U.S. Government Printing Office, Washington, DC.

Norris, J.C., S.J.Moore, and A.S.Hume. 1986. Synergistic lethality induced by combination of carbon monoxide and cyanide. Toxicology 40(2):121–130.

NRC (National Research Council). 2000. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

O'Flaherty, E.J., and W.C.Thomas. 1982. The cardiotoxicity of hydrogen cyanide as a component of polymer pyrolysis smokes. Toxicol. Appl. Pharmacol. 63(3):373–381.

Okoh, P.N. 1983. Excretion of 14C-labeled cyanide in rats exposed to chronic intake of potassium cyanide. Toxicol. Appl. Pharmacol. 70(2):335–339.

Peden, N.R., A.Taha, P.D.McSorley, G.T.Bryden, I.B.Murdoch, and J.M.Anderson. 1986. Industrial exposure to hydrogen cyanide: Implications for treatment. Br. Med. J. 293(6546):538.

Potter, A.L. 1950. The successful treatment of two recent cases of cyanide poisoning. Br. J. Ind. Med. 7:125–130.

Pryor, A.J., D.E.Johnson, and N.N.Jackson. 1975. Hazards of smoke and toxic gases produced in urban fires. J. Fire Flammability/Combust. Toxicol. (Suppl. 2):64–112.

Purser, D.A., P.Grimshaw, and K.R.Berrill. 1984. Intoxication by cyanide in fires: A study in monkeys using polyacrylonitrile. Arch. Environ. Health 39(6):394–400.

Sakurai, T. 1989. Toxic gas tests with several pure and mixed gases using mice. J. Fire Sci. 7(1)22–77.

Singh, B.M., N.Coles, P.Lewis, R.A.Braithwaite, M.Nattrass, and M.G.FitzGerald. 1989. The metabolic effects of fatal cyanide poisoning. Postgrad. Med. J. 65(770):923–925.

Vernot, E.H., J.D.MacEwen, C.C.Haun, and E.R.Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2):417–423.

Walton, D.C., and M.G.Witherspoon. 1926. Skin absorption of certain gases. J. Pharmacol. Exp. Ther. 26:315–324.

Weast, R.C., M.J.Astle, and W.H.Beyer, eds. 1985. Pp. D-165 in CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data, 66th Ed. Boca Raton: CRC.

Wolfsie, J.H., and C.B.Shaffer. 1959. Hydrogen cyanide. Hazards, toxicology, prevention and management of poisoning. J. Occup. Med. 1:281–288.

Wood, J.L., and S.L.Gooley. 1956. Detoxication of cyanide by cystine. J. Biol. Chem. 218:449–457.

Wurzburg, H. 1996. Treatment of cyanide poisoning in an industrial setting. Vet. Hum. Toxicol. 38 (1):44–47.

Yamamoto, K., Y.Yamamoto, H.Hattori, and T.Samor. 1982. Effects of routes of administration on the cyanide concentration distribution in the various organs of cyanide-intoxicated rats. Tohoku J. Exp. Med. 137:73–78.

7

Hydrogen Sulfide

This chapter reviews the physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on hydrogen sulfide. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine from exposure to hydrogen sulfide and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to hydrogen sulfide.

BACKGROUND INFORMATION

Hydrogen sulfide is a colorless, flammable gas at ambient temperature and pressure. It is an irritant and asphyxiant and has an offensive odor similar to rotten eggs. It has been reported that people can smell hydrogen sulfide at concentrations as low as 0.5 parts per billion (ppb) of air (ATSDR 1999). Hydrogen sulfide has an odor threshold of 0.02–0.13 parts per million (ppm) (Beauchamp et al. 1984). Olfactory fatigue (which causes a loss of odor perception) can occur at 100 ppm, and paralysis of the olfactory nerve has been reported at 150 ppm (Beauchamp et al. 1984). The chemical and physical properties of hydrogen sulfide are summarized in Table 7–1.

TABLE 7–1 Physical and Chemical Properties for Hydrogen Sulfide

Characteristic	Value
Common name	Hydrogen sulfide
Synonyms	Hydrosulfuric acid, sulfuric hydride, sulfurated hydrogen, dihydrogen monosulfide, dihydrogen sulfide, stink damp, sewer gas
Chemical formula	H_2S
Chemical structure	H-S-H
CAS number	7783–06–4
Molecular weight	34.08
Physical state	Colorless gas
Odor threshold	0.02–0.13 ppm
Freezing point	–85.49°C
Boiling point	–60.33°C
Flash temperature	26°C
Flammable limits in air	4.3–46% by volume
Vapor pressure	10.8 atm (0°C), 18.5 atm (20°C)
Specific gravity	1.192
Density	1.5392 g/L at 0°C, 760 mmHg
Solubility	1 g in 242 mL water at 20°C; soluble in alcohol, ether, glycerol, gasoline, kerosene, crude oil, and carbon dioxide
Conversion factors in air	1 ppm=1.40 mg/m^3 1 mg/m^3=0.7 ppm

Abbreviations: CAS, Chemical Abstract Service.
Sources: Beauchamp et al. (1984); NRC (1985); ATSDR (1999).

Hydrogen sulfide has been widely used as a reagent in analytical chemistry. Its major use is in the production of elemental sulfur and sulfuric acid (ATSDR 1999). It is also used in the manufacture of heavy water for the nuclear energy industry, in the production of sodium sulfide and thiophenes, in rayon manufacturing, as an agricultural disinfectant, and as an additive in lubricants.

Most of the hydrogen sulfide in the atmosphere—approximately 90%— comes from natural sources through nonspecific and anaerobic bacterial reduction of sulfates and sulfur-containing organic compounds (ATSDR 1999). These sources include stagnant or polluted waters and manure or coal pits with low

oxygen content. Other natural sources include volcanoes, some plant species, and oceans. Hydrogen sulfide generated by anaerobic bacterial reduction also can be emitted by waste water treatment plants or landfills. Hydrogen sulfide is produced by colonic bacteria in humans and animals and has been measured at 0.01– 30 ppm in flatulus of healthy humans (Suarez and Levitt 1999). Studies in rats indicate that very high concentrations (1,000 ppm) of hydrogen sulfide produced in the cecum are detoxified by the colonic mucosa, thereby reducing the amount present in rectal gas (Suarez and Levitt 1999). Human exposure to hydrogen sulfide can come from natural sources, from its intentional use in industrial processes, and from its release as a byproduct of processes involving sulfur-containing chemicals (NRC 1985).

TOXICOKINETIC CONSIDERATIONS

Hydrogen sulfide is primarily absorbed through the lungs; however, it also can be absorbed through the gastrointestinal tract and intact skin (Laug and Draize 1942; Wetterau et al. 1964, as cited in ATSDR 1999). The remainder of this section summarizes data on the absorption, distribution, metabolism, and excretion of hydrogen sulfide.

Absorption

Inhalation is the most common route of hydrogen sulfide exposure. Hydrogen sulfide is absorbed rapidly through the lungs (ATSDR 1999). It dissociates at physiologic pH to the hydrogen sulfide anion (Lide 1991), which is probably the absorbed form (WHO 1987). The absorption of hydrogen sulfide in humans and animals has not been quantitatively characterized.

No studies were found that examined absorption in humans after dermal exposure to hydrogen sulfide. There are few experimental animal studies examining absorption of hydrogen sulfide after dermal exposure. Laug and Draize (1942) reported that absorption of hydrogen sulfide did occur when rabbits were subject to dermal exposure to undetermined concentrations of hydrogen sulfide. Lethality and a positive sulfide reaction of expired air with lead acetate paper were observed. Dermal absorption was not observed in 2 guinea pigs exposed to hydrogen sulfide (concentration undetermined) for 1 h on a small area of shaved skin (Walton and Witherspoon 1925). However, when the entire torso of guinea pigs was exposed to hydrogen sulfide, the animals died after approximately 45 min, indicating dermal exposure. Dermal exposure was not apparent

after a dog received full-body treatment (not including head) to undetermined concentrations of hydrogen sulfide (Walton and Witherspoon 1925).

Distribution

Human data are sparse on the tissue distribution after inhalation exposure to hydrogen sulfide. One case report identified sulfide in the tissues of 3 men who drowned after being overcome, possibly, by exposure to hydrogen sulfide and fell into a lake (Kimura et al. 1994). The actual concentration of hydrogen sulfide is not known, but was estimated at 550–650 ppm, based on extrapolation of tissue concentrations from rat studies (Kimura et al. 1994; Nagata et. al 1990). Sulfide was measured in the blood, brain, lungs, liver, spleen, and kidney of the individuals (0.08–0.2, 0.2–1.06, 0.21–0.68, 1.3–1.56, 0.32–0.64, 0.47–1.5 μg/g tissue, respectively). A second case report identified hydrogen sulfide concentrations of 0.92 μg/g (micrograms per gram) in blood, 1.06 μg/g in brain, 0.38 μg/g in liver, and 0.34 μg/g in kidney at autopsy in a man who was overcome by hydrogen sulfide in a tank that contained 1,900–6,100 ppm (Winek et al. 1968).

Studies conducted with animals have shown that distribution of inhaled hydrogen sulfide is rapid and widespread. Hydrogen sulfide (concentration not reported) was found in the brain, liver, kidneys, pancreas, and small intestine of rats and guinea pigs exposed by inhalation for times ranging from 1 min to 10 h (Voigt and Muller 1955, as cited in Beauchamp et al. 1984). In another study, rats were exposed by inhalation to 550 or 650 ppm hydrogen sulfide until death (Nagata et al. 1990). Blood, liver, and kidneys had an increase in sulfide concentration with time after death (whether exposed or not), whereas lung, brain, and muscle showed little change in sulfide concentration. Distribution of hydrogen sulfide did not change relative to duration of exposure when rats were exposed by inhalation to 75 ppm for 20, 40, or 60 min (Kohno et al. 1991, as cited in ATSDR 1999). In this study, 10 μg/mL was measured in blood, 25 μg/g in brain, 20 μg/g in lung, 37 μg/g in heart, 20 μg/g in liver, 25 μg/g in spleen, and 30 μg/g in kidney. Thiosulfate was found in blood (0.08 μmol/mL), lung (0.095 μmol/g), and brain (0.023 μmol/g) of rabbits exposed by inhalation at concentrations of 500–1,000 ppm hydrogen sulfide for an average of 22 min (Kage et al. 1992). Little or no thiosulfate was found in the kidney, liver, and muscle. The authors used thiosulfate as a marker for hydrogen sulfide exposure and concluded that it is a better marker than sulfide.

No studies were found that examined tissue distribution in humans or animals after dermal exposure to hydrogen sulfide.

Metabolism

Although distribution of hydrogen sulfide is rapid and widespread, tissue accumulation is limited by rapid metabolism and excretion (reported half-life in the body of 60 min; Milby and Baselt 1999). Hydrogen sulfide is metabolized through 3 pathways: oxidation of the sulfide to sulfate, methylation of hydrogen sulfide to produce methanethiol and dimethylsulfide, and reaction of hydrosulfide with metallo- or disulfide-containing enzymes (reviewed in Beauchamp et al. 1984). The major metabolic pathway is oxidation in the liver; however, the exact mechanism is not known. It is known that hydrogen sulfate is oxidized to free sulfate or conjugated sulfate and is excreted in the urine (Beauchamp et al. 1984). Methylation of hydrogen sulfide is thought to be catalyzed by thiol S-methyl-transferase, yielding less toxic methanethiol and dimethylsulfide (Beauchamp et al. 1984). One review noted that 10% or more of the population could be genetically deficient in the ability to metabolize organosulfides (Guidotti 1994). Such persons excrete sulfur compounds through the skin or by exhalation.

Hydrogen sulfide reacts with metalloproteins found in several enzymes. It causes toxicity by interrupting the electron transport chain through inhibition of cytochrome oxidase, leading to compromised oxidative phosphorylation and aerobic metabolism, increased peripheral tissue pO_2 (partial pressure of oxygen), and decreased unloading gradient for oxyhemoglobin. These events lead to increased concentrations of oxyhemoglobin in the venous return, resulting in flushed skin and mucous membranes. Lactic acidemia occurs as a result of the increased demand placed on glycolysis. The affinity of hydrogen sulfide for cytochrome oxidase is believed to be in the same order of magnitude as that of cyanide (Wever et al. 1975).

No studies were found that examined metabolismin humans or animals after dermal exposure to hydrogen sulfide.

Elimination

After sulfide is oxidized to sulfate (the major metabolic pathway), sulfate is excreted in the urine (Beauchamp et al. 1984). A human volunteer exposed at a concentration of 18 ppm hydrogen sulfide for 30 min was found to have urinary thiosulfate concentrations of approximately 2, 4, 7, 30, and 5 μmol/mM creatine 1, 2, 5, 15, and 17 h after exposure, respectively (Kangas and Savolainen 1987). Blood thiosulfate concentrations decreased in rabbits exposed to hydrogen sulfide at a concentration 100–200 ppm for 60 min from 0.061 μmol/mL immediately after exposure to an undetectable amount after 4 h (Kage et al. 1992). Urine

samples from the same animals showed that thiosulfate concentrations were highest (1.2 μmol/mL) 1–2 h after exposure and were still detectable 24 h after exposure at a slightly higher concentration than shown in controls.

No studies were found that examined excretion in humans after dermal exposure to hydrogen sulfide. One study conducted in rabbits provides evidence of excretion of hydrogen sulfide after dermal exposure (Laug and Draize 1942). The fur on the trunk of the animals was clipped, left intact, or abraded and then the animals were exposed to hydrogen sulfide (concentration not reported) for 1.5–2 h. The animals were then exposed to clean air. Expired air from the animals reacted with lead acetate paper, indicating the presence of sulfide (Laug and Draize 1942).

HUMAN TOXICITY DATA

Hydrogen sulfide at high concentrations is extremely toxic to humans and at concentrations greater than 700 ppm in air can be rapidly fatal (Beauchamp et al. 1984). Hydrogen sulfide is known to have 2 major effects in humans: local inflammation and irritation of moist membranes, including the eye and deeper parts of the respiratory tract; and respiratory paralysis and unconsciousness ("knockdown") potentially leading to death (Beauchamp et al. 1984; Reiffensten et al. 1992). The former effects occur at lower air concentrations; the latter are caused by high concentrations. Because hydrogen sulfide is rapidly metabolized, it is not considered a cumulative toxicant (Beauchamp et al. 1984; Milby and Baselt 1999). This section reviews human toxicity data on hydrogen sulfide from experimental studies, accidental exposures, occupational studies, and epidemiology studies. The data are summarized in Table 7–2.

Experimental Studies

Several studies in humans have examined inhalation of hydrogen sulfide at low concentrations (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a,b, 1997; Jäppinen et al. 1990). The data are summarized in Table 7–2.

One study found that exposing healthy men to 5.0 ppm hydrogen sulfide for up to 16 min during graded exercise resulted in a significant increase in maximum oxygen uptake, a significant decrease in carbon dioxide output, and a significant increase in blood lactate compared with controls (Bhambhani and Singh 1991). However, maximal power output was not affected and thus the biologic and toxicologic significance of these effects in not known. No treatment-related

TABLE 7-2 Human Toxicity Data, Inhalation Exposure to Hydrogen Sulfide

Subjects	Route	Concentration (ppm)	Duration	Effects	Reference
EXPERIMENTAL	STUDIES				
10 asthma patients (3 men aged 33-50; 7 women aged 31-61)	Inhalation	2 ppm	30 min	All subjects complained of unpleasant odor, nasal and pharyngeal dryness; 3 of 10 complained of headache. No significant effects on FVC, FEV_1, FEF; average increase of 26.3% in Raw (no accompanying clinical signs were observed). Average decrease of 8.4% in SGaw (changes in Raw and SGaw insignificant, but 2 of 10 subjects showed changes in excess of 30% in both Raw and SGaw).	Jäppinen et al. 1990
16 healthy males (aged 25.2 ± 5.5), experiment performed during graded exercise to exhaustion	Inhalation	0.0, 0.5, 2.0, or 5.0 ppm	Up to 16 min	No treatment-related effects on heart rate, expired ventilation during submaximal or maximal exercise. At 5.0 ppm, significant ($P < 0.05$) increase in oxygen uptake, significant ($P < 0.05$) decrease in carbon dioxide output, significant ($P < 0.05$) increase in blood lactate. Maximal power output unaffected.	Bhambhani and Singh 1991
25 healthy individuals (13 men age 24.7 ± 4.6 and 12 women age 22 ±	Inhalation	0.0, 5.0 ppm	30 min	No treatment-related effects in men or women on oxygen uptake, carbon dioxide production, respiratory exchange ratio, heart rate, blood pressure, arterial blood	Bhambhani et al. 1994; 1996a

2.1), experiment performed while subjects were exercising on a cycle ergonometer at 50% of VO_{2MAX}				oxygen and carbon dioxide tensions or pH, perceived exertion ratings. Treatment-related effects in men: muscle citrate synthetase decreased 19% ($P < 0.05$), muscle lactate and lactic acid dehydrogenase increased 24% (NS)and 6% (NS), respectively; cytochrome oxidase decreased 9%(NS). Treatment-related effects in women: muscle citrate synthetase decreased 19% (NS), cytochrome oxidase increased 23% (NS), muscle lactate and lactic acid dehydrogenase affected. Subjects reported no adverse health effects after exposure.	
19 healthy individuals (9 men aged 23.4 ± 6.4 10 women aged 21.8 ± 3.0), experiment was performed while subjects were exercising on a cycle ergonometer at 50% of VO_{2MAX}	Inhalation	0.0, 10.0 ppm	15 min	No treatment-related effects in men or women on FVC, FEV_1, peak expiratory flow rate, forced expiratory flow rate, or maximal ventilation volume.	Bhambhani et al. 1996b

Subjects	Route	Concentration (ppm)	Duration	Effects	Reference
28 healthy individuals (15 men age 23.4 ± 5.2 and 13 women age 21.8 ± 3.0), experiment was performed while subjects were exercising on a cycle ergonometer at 50% of VO_{2MAX}	Inhalation	0.0 or 10.0 ppm	30 min × 2	Significant ($P < 0.05$) decrease in oxygen uptake and increase in blood lactate observed in men and women compared with controls. No treatment-related effects in men and women on carbon dioxide production, respiratory exchange ratio, heart rate, blood pressure, arterial blood oxygen, carbon dioxide tensions. Treatment-related effects in men: muscle lactate increased 33% (NS), muscle cytochrome oxidase decreased 16% (NS). Treatment-related effects in women: muscle lactate increased 16% (NS), muscle cytochrome oxidase increased 11% (NS). Subjects reported no adverse health effects after exposure.	Bambhani et al. 1997
ACCIDENTAL EXPOSURES					
4 men entered a liquid manure storage pit	Inhalation	76 ppm detected in air samples 1 wk after accident; concentrations probably higher at time	NR	Unconsciousness occurred within a few minutes; 3 men died before reaching the hospital; autopsy showed massive liquid manure pulmonary aspiration in 2 men and fulminant pulmonary edema without manure aspiration in 1; increased heart-blood sulfide found; the surviving patient	Osbern and Crapo 1981

		of exposure		had hemodynamic instability, respiratory distress syndrome, infection.	
2 individuals entered a sewer manhole	Inhalation	200 ppm detected 6 d after accident	45 min	Both individuals collapsed and died.	NIOSH 1991
1 individual exposed at a poultry processing plant	Inhalation	2,000-4,000 ppm (estimated)	15-20 min	Pulmonary, intracranial, and cerebral edema, and cyanosis observed at autopsy.	Breysse 1961
10 Individuals	Inhalation	429 ppm 4 h after accident	NR	5 individuals died at site of exposure; 4 lost consciousness after 2-20 min and were in a deep coma for approximately 48 h (they were given hyperbaric oxygen therapy); electrocardiograms showed T-wave changes in all survivors and P-wave change in survivor. EEGs normal in all but 1 survivor by 9 d after accident; EEG normal in the last survivor by day 36. No pulmonary edema or long-term neurological abnormalities identified .	Hsu et al. 1987
16-yr-old boy 10 m away from underground liquid manure storage tank, in which the contents had been agitating	Inhalation	>60 ppm (Equipment detection limit) 2 d later	NR	Individual began coughing, then vomited, lost consciousness, and died. Autopsy showed tracheobronchial aspiration of stomach contents, focal pulmonary hemorrhages and edema, small petechial brain hemorrhage.	Morse et al. 1981

Subjects	Route	Concentration (ppm)	Duration	Effects	Reference
6 individuals	Inhalation	NR	5-20 min	Examined 5-10 yr after accidental exposure and had persistent neurologic symptoms including impaired vision, memory loss, decreased motor function, tremors, ataxia, abnormal learning and retention, slight cerebral atrophy. One individual severely demented.	Tvedt et al. 1991 a,b
37 individuals (aged 24-50) exposed while drilling a pit to lay the foundation for a sewage pumping station	Inhalation	NR	NR	Workers reported headaches, dizziness, breathlessness, cough, burning discomfort in the chest, throat and eye irritation, nausea, vomiting. 1 worker died, another was in a coma for 5 d, remaining 35 workers recovered with no lasting effects. 18 mo after exposure, the worker who had been comatose showed slow speech, impaired attention span, easily distracted, isolated retrograde amnesia, decreased ability to communicate, impaired visual memory, and poor retention of new information	Snyder et al. 1995
OCCUPATIONAL STUDIES					
26 male pulp mill workers (mean age 40.3)	Inhalation	Usually below the maximum permitted	Likely ex.: 8 h/day, 5	No significant changes in respiratory function or bronchial responsiveness observed compared with controls.	Jäppinen et al. 1990

		concentration of 10 ppm	d/wk		
175 oil and gas workers (mean age 35)	Inhalation	Exposure concentration not known; 51 workers reported "exposures strong enough to cause symptoms," 14 workers reported "exposures that resulted in loss of consciousness," 110 workers reported "no exposure"	NR	Exposures strong enough to cause symptoms not associated with lower spirometric values; exposures that resulted in loss of consciousness also not associated with lower spirometric values, but associated with shortness of breath, wheezing with chest tightness, and wheezing attacks.	Hessel et al. 1997
21 swine confinement facility owners or operators	Inhalation	Not reported	5 h/wk	Statistically significant ($P < 0.05$) decrease in FEF (3.3-11.9%) after a 4-h work period.	Donham et al. 1984
Sewer treatment facility workers (water treatment workers who are	Inhalation	Exposure concentration not known; workers	NR	Significant differences between FEV_1/FVC of high-exposure sewer and water treatment workers. Prevalence odds ratio for obstructive lung disease 21.0 (95%	Richardson 1995

Subjects	Route	Concentration (ppm)	Duration	Effects	Reference
not exposed to hydrogen sulfide used as a comparison group		categorized into high-, medium-, and low-exposure groups based on job description		CI = 2.4-237.8) in nonsmoking sewer workers with presumed high hydrogen sulfide exposure when compared with nonsmoking water treatment workers. Prevalence odds ratio for sewer workers who smoke versus water treatment workers who smoke was 1.7 (95% CI = 0.2-13.6).	
123 "overexposed" workers in a heavy-water plant	Inhalation	NR	Exposed on the job 15 yr; over-exposures likely resulted from acute high-dose incident	42 became unconscious. Most frequently reported acute effects: weakness, nausea, dizziness, headache, nervousness. Delayed effects: nervousness, headache, nausea, insomnia. Eye irritation relatively less common (11 workers reported acute effects, 3 reported delayed effects).	Poda 1966
6,500 occupational cases of "spinner's eye" (most frequently noted in viscose rayon	Inhalation	11 ppm	6-7 h	First symptoms of eye irritation occurred.	Nesswetha 1969
		14 ppm	4-5 h	"Eye diseases" began to develop after this time period.	

manufacturing plants)				The author noted that carbon disulfide exposure, which is common in the industry, is a strong sensitizing factor and that the widespread belief that the localized irritating effects of hydrogen sulfide alone causes "spinner's eye" does not seem to be correct.	
EPIDEMIOLOGY STUDIES					
Communities near pulp mills	Inhalation	"Severely polluted" community: mean 2.9 ppb, maximum 4 h 40 ppb; "moderately polluted" community: mean 1.4 ppb, maximum 4 h 16 ppb.	Daily	Occurrence of nasal symptoms, cough, breathlessness, and wheezing found significantly greater in individuals living in the polluted communities compared with a non-polluted community. Increase in symptoms was dose related (based on comparison of prevalence of symptoms among the three communities; communities were exposed to relatively high concentrations of other malodorous sulfur compounds in addition to hydrogen sulfide.	Jaakkola et al. 1990 (South Karelia Air Pollution Study)
Small community near pulp mill	Inhalation	Daily mean total reduced sulfur concentrations: 0-82 $\mu g/m^3$, monthly mean concentration: 3-19 $\mu g/m^3$	Daily	Dose-related increase in nasal and pharyngeal irritation. Probability ratios for medium and high exposures: 3.13 (95% CI 1.25-7.25) and 8.5 (95% CI 3.19-18.64) (nasal symptoms) and 2.0 (95% CI 0.92-4.14) and 5.20 (95% CI 1.95-1.99) (pharyngeal irritation). Contribution of hydrogen sulfide to health effects unclear.	Marttila et al. 1995 (South Karelia Air Pollution Study)

Subjects	Route	Concentration (ppm)	Duration	Effects	Reference
Communities near pulp mills	Inhalation	Mean annual total reduced sulfur concentrations: 2-3 $\mu g/m^3$, 24-h average concentration: 0-56 $\mu g/m^3$, maximum 1-h concentration: 155 $\mu g/m^3$	Daily	Reported increased incidence of respiratory system symptoms (irritation, cough) and CNS symptoms (headache and migraine); significant increase only for headache and migraine. Communities exposed to relatively high concentrations of other malodorous sulfur compounds.	Partti-Pellinin et al. 1996 (South Karelia Air Pollution Study)

Abbreviations: CI, confidence interval; CNS, central nervous system; EEG, electroencephaologram; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF, forced expiratory flow; $\mu g/m^3$, micrograms per cubic meter; NR, not reported; ppb, parts per billion; Raw, airway resistance; SGaw, specific airway conductance; VO_{2MAX} maximum oxygen uptake.

effects on heart rate or expired ventilation during submaximal or maximal exercise were reported in men exposed to 0.5 or 2.0 ppm hydrogen sulfide (Bhambhani and Singh 1991).

In another study, healthy men and women were exposed to 5.0 ppm hydrogen sulfide for 30 min while exercising on a cycle ergometer (Bhambhani et al. 1994). Inhalation of 5.0 ppm hydrogen sulfide had no significant effect on any of the measured physiologic or perceptual responses after 30 min of submaximal exercise when compared with controls. There was a trend (not significant) for the hydrogen sulfide exposure to induce mild hypertension during exercise in men and in women. Biopsies were obtained from the subjects' vastus lateralis muscles and analyzed to determine whether exposure affected anaerobic or aerobic metabolism (Bhambhani et al. 1996a). The only significant finding was a decrease in citrate synthetase concentration in men exposed to 5.0 ppm hydrogen sulfide. There were no significant changes in the concentrations of muscle lactate, lactate dehydrogenase, and cytochrome oxidase. Bhambhani et al. (1996b) exposed healthy men and women to 10.0 ppm hydrogen sulfide for 15 min during exercise on a cycle ergometer. The authors concluded that there were no significant changes in pulmonary function between the group exposed to hydrogen sulfide and the control group. The variables measured were forced vital capacity, forced expiratory volume in 1 s, the ratio of forced expiratory volume in 1 s to forced vital capacity, peak expiratory flow rate, forced expiratory flow, maximum ventilation volume, and diffusion capacity of the lung for carbon monoxide. In a follow-up study, Bhambhani et al. (1997) examined the cardiovascular, metabolic, and biochemical responses of healthy men and women after exposure to 10.0 ppm hydrogen sulfide for two 30-min exercise sessions on a cycle ergometer. The most significant finding of this study was that inhalation of 10 ppm hydrogen sulfide decreased oxygen uptake during submaximal exercise. The study authors attribute this decrease to a tendency for aerobic metabolism to be inhibited in the exercising muscle.

Jäppinen et al. (1990) exposed 10 subjects who had asthma to 2 ppm hydrogen sulfide for 30 min. On average, airway resistance was increased by 26.3% and specific airway conductance was decreased by 8.4% in the exposed subjects compared with control subjects. Although the changes were not statistically significant, 2 subjects showed changes of more than 30% in airway resistance and specific airway conductance, which indicate bronchial obstruction (Jäppinen et al. 1990).

Accidental Exposures

Several case reports have been made of accidental inhalation exposure to hydrogen sulfide (summarized in ATSDR 1999). However, in most cases, the

concentration and duration of exposure are unreported or are estimated. Several case reports involving accidental exposure to hydrogen sulfide are summarized in Table 7–2.

Fuller and Suruda (2000) report that 80 fatalities in 57 incidents occurred in the United States from 1984 to 1994. Nineteen fatalities and 36 injuries occurred in those attempting to rescue an incapacitated worker (Fuller and Suruda 2000). In most fatal cases of exposure to hydrogen sulfide, the concentration was probably more than 500 ppm (Beauchamp et al. 1984). At sufficiently high concentrations, some persons lose consciousness after inhaling only 1 or 2 breaths of hydrogen sulfide. This is called the "slaughterhouse sledgehammer effect." Fatalities as a result of hydrogen sulfide exposure usually occur in confined spaces, such as sewers, animal containment facilities, waste dumps, sludge plants, manure tanks, and cesspools (ATSDR 1999). Workplace fatalities also have occurred in the petroleum and natural gas industries from hydrogen sulfide (Fuller and Suruda 2000). Death occurs as a result of respiratory failure, initially presenting with respiratory insufficiency, noncardiogenic pulmonary edema, coma, and cyanosis (ATSDR 1999; Breysse 1961; Hsu et al. 1987; Morse et al. 1981; NIOSH 1991; Osbern and Crapo 1981). Other effects include ocular and respiratory tract irritation, nausea, headache, loss of equilibrium, memory loss, olfactory paralysis, cardiac abnormality, loss of consciousness, tremor, and convulsion (ATSDR 1999; Hsu et al. 1987; Osbern and Crapo 1981; Snyder et al. 1995; Tvedt et al. 1991 a,b)

The mechanism by which hydrogen sulfide causes respiratory paralysis, unconsciousness, and apnea is not completely understood. A commonly cited mechanism is inhibition of cytochrome oxidase, thereby affecting the respiratory motor cells in the cerebellum (Beauchamp et al. 1984). Other possibilities advanced are hyperpolarization of neurons in the respiratory center of the brain via increased conductance of ion channels (Reiffenstein et al. 1992), effects on the carotid and aortic chemoreceptors (Ammann 1986), and induction of apnea from an afferent neural signal from the lung via the vagus (Almeida and Guidotti 1999). Inhibition of cytochrome oxidase or induction of apnea, however, would not occur fast enough to account for the immediate respiratory paralysis and unconsciousness observed at high concentrations that occurs with only a breath or two. Thus, more than one mechanism is likely involved in inducing the effects of hydrogen sulfide at high doses.

Occupational Studies

Several occupational studies have examined inhalation exposure to hydrogen sulfide (Donham et al. 1984; Hessel et al. 1997; Richardson 1995) (Table 7–2).

Respiratory effects, such as shortness of breath while hurrying up a slight hill, wheezing with chest tightness, and wheezing attacks, were observed in oil and gas workers who reported that they were exposed to concentrations of hydrogen sulfide that resulted in loss of consciousness (Hessel et al. 1997). Those workers did not have lower spirometric values when compared with controls. The concentration of hydrogen sulfide to which they were exposed is not known (Hessel et al. 1997). Donham et al. (1984) reported a significant decrease ($P<0.05$) in forced expiratory flow among workers in a swine confinement facility after they had worked a 4 h shift. Jäppinen et al. (1990) found no significant changes in respiratory function or bronchial responsiveness relative to controls in 26 male pulp mill workers who had daily hydrogen sulfide exposure at usually less than 10 ppm. Richardson (1995) compared spirometric values between sewer treatment facility workers (exposed to hydrogen sulfide, concentrations not reported) and water treatment facility workers (not exposed). The exposed workers were categorized into low-, medium-, and high-exposure groups based on job description. There was a significant difference in the ratio of forced expiratory volume in 1 s to forced vital capacity between sewer treatment facility workers in the high-exposure group and water treatment facility workers (Richardson 1995).

Poda (1966), reporting on symptoms of overexposure to hydrogen sulfide among workers at a heavy-water plant, listed acute effects of weakness, nausea, dizziness, headache, and nervousness. Eye irritation also was reported, but not as frequently as other effects were. The concentrations causing overexposure were not reported, but 42 of 123 persons were exposed to concentrations high enough to cause unconsciousness.

Poda (1966) also reported that persons with perforated eardrums can be exposed even when wearing a self-contained breathing apparatus because hydrogen sulfide can enter the body though the ear and presumably reach the respiratory tract. Nevertheless, Ronk and White (1985) state that this observation is not supported by calculations of the amount of hydrogen sulfide leakage for a variety of eustacian tube conditions, by the medical literature, or by other personal reports. Ronk and White (1985) thus recommend that persons who have perforated eardrums not be excluded from working in a hydrogen sulfide environment.

Epidemiologic Studies

Several epidemiologic studies have examined the health effects of inhalation exposure to sulfur compounds (e.g., Jaakkola et al. 1990; Marttila et al. 1995; Partti-Pellinen et al. 1996; other studies summarized in ATSDR 1999). The first three studies are part of the South Karelia air pollution study (Table 7–2). In general, the studies report that exposure to sulfur dioxide and other sulfur com

pounds from pulp mills causes respiratory symptoms, such as nasal and pharyngeal irritation, cough, breathlessness, and wheezing and CNS symptoms, such as headache and migraine. However, because exposure is to several sulfur compounds, including sulfur dioxide, hydrogen sulfide, methyl mercaptan, and methyl sulfides, it is not possible to determine the contribution of hydrogen sulfide to specific respiratory or CNS effects.

Exposure that causes these community-wide symptoms also is poorly quantified. Health effects could be more related to short-term peak concentrations in the community (e.g., due to wind shifts) than to the longer term averages that typically are measured. The reported health symptoms are also difficult to separate from effects that could result because of the annoyance from the bad smell of hydrogen sulfide and because of anger directed toward the source of pollution.

Because of such problems with studies of communities, and the availability of more carefully controlled human experimental and occupational studies, community studies are less appropriate for assessing the Navy's proposed SEALs. Community exposures also generally occur over longer periods than those considered by the SEALs. Therefore, not all of the available community studies are reviewed and presented here.

Summary of Human Toxicity Data

Based on the above-described studies and summary reports of Beauchamp et al. (1984), WHO (1987), ACGIH (1991), Reiffenstein et al. (1992), Guidotti (1994, 1996), and ATSDR (1999), the major clinical health effects of hydrogen sulfide are summarized in Table 7–3 in order of increasing exposure concentrations. The exposure duration for these effects is generally short-term (i.e., less than an hour to a few days in the work place). The exposure duration is often difficult to determine because although workers may be exposed to hydrogen sulfide for years, many of the effects noted—particularly at higher concentrations—result from relatively short-term exposures due to short-term peak concentrations from an incident that occurred in the work place. Additionally, in some cases, the peak levels associated with the effects may not have been recorded (see accidental exposure studies cited in Table 7–2). The literature often does not report the duration of exposure or provides only general information such as "prolonged exposure." Another factor that complicates the evaluation of exposure duration for effects is that although irritant effects of hydrogen sulfide may develop within minutes, some adaptation to the irritant effects of hydrogen sulfide may occur with continued exposure.

TABLE 7–3 Summary of Human Toxicity Data

Concentration (ppm)	Effect
≤1	Possible eye irritation and subjective effects (e.g., headache, nausea) reported in residential communities near hydrogen sulfide sources. Exposure causing the problems are uncertain because measurements often are of long-term averages rather than short-term peaks.
2	2 of 10 subjects with asthma had increased airway resistance, decreased airway conductance during exercise (30-min exposure; Jäppinen et al. 1990).
5–10	Minor changes signifying effects on aerobic capacity of exercising muscle in healthy exercising subjects (2 15- or 30min exposure periods. Other parameters unaffected, no effect on respiratory function.
≤10	No significant respiratory function or bronchial responsiveness relative to controls in workers continually exposed in the workplace (Jäppinen et al. 1990). Reported to be protective of eye irritation in the workplace (ACGIH 1998).
5–20	Eye irritation and lacrimation with concomitant exposure to other chemicals (carbon disulfide) or irritants (acids) in the workplace.
20–50	Eye irritation, lacrimation, lung irritation; possible eye damage after several days' exposure (Guidotti 1994); possible digestive upset and loss of appetite.
100–150	Olfactory fatigue, paralysis of olfactory nerve.
50–300	Respiratory irritation, pneumonia from prolonged exposure, acute conjunctivitis, pain lacrimation, photophobia progressing to keratoconjunctivitis, vesiculation of the corneal epithelium, pulmonary edema with prolonged exposure at 250 ppm.
300–500	Respiratory effects, pulmonary edema.
500–1,000	Within minutes, CNS stimulation, hyperpnea leading to apnea, convulsions, unconsciousness, and death. Within 30 min, severe eye and lung damage.
1,000–2,000	Immediate respiratory center paralysis, rapid unconsciousness, death.

EXPERIMENTAL ANIMAL TOXICITY DATA

Numerous experimental animal studies have examined hydrogen sulfide toxicity. Many of them are summarized below and in Table 7–4. Most animal studies have examined effects at doses well above the proposed SEALs of 10 and 20 ppm. Less information available about the range of lower concentrations that cause eye irritation. The results of the animal studies reviewed are generally consistent with the human data.

Acute Exposure

Several laboratories examined animal lethality from inhalation exposure to hydrogen sulfide. The concentration that is lethal to 50% of study animals (LC_{50}) calculated for the rat ranges from 683 to 835 ppm for exposures up to 1 h (Arts et al. 1989; Zwart et al. 1990) and from 335 to 587 ppm for exposures of 2–6 h (Prior et al. 1988; Tansy et al. 1981). All Sprague-Dawley rats exposed at approximately 1,655 ppm died after 3 min (Lopez et al. 1989). All Fischer 344 rats exposed at 500 to 700 ppm for 4 h died, but Fischer 344 rats exposed at 400 ppm for the same period did not die (Khan et al. 1990; Lopez et al. 1987, 1988 a,b). All Wistar rats exposed at 800 ppm for 12 min died (Beck et al. 1979), but Wistar rats exposed at 500 ppm for 2 h did not die (Higuchi 1977). Mouse LC_{50} range from 634 to 1,160 ppm for exposures up to 1 h. No deaths were reported in CB-20 and NMRI mice exposed at 100 ppm for 2 h to 4 d (Elovaara et al. 1978; Savolainen et al. 1980). Smith and Gosselin (1964) reported that all CD 1 mice exposed at 722 ppm for 50 min and at 1,872 ppm for 10 min died. Japanese white rabbits exposed at concentrations ranging from 500 to 1,000 ppm for 30 min died (Kage et al. 1992).

The major systems affected by acute exposure to hydrogen sulfide are the respiratory and nervous systems. There is also some evidence of ocular and cardiovascular toxicity. Fischer 344 rats exposed at 400 ppm for 4 h showed the presence of nasal cavity lesions and decreased bronchoalveolar cell counts (Green et al. 1991; Khan et al. 1991; Lopez et al. 1987, 1988a). Enzyme activity changes (e.g., lactate dehydrogenase, alkaline phosphatase, cytochrome c oxidase, succinate oxidase) were observed in Fischer 344 rats exposed at 50–400 ppm for 4 h (Green et al. 1991; Khan et al. 1990; Lopez et al. 1987, 1988a). The lungs of Fischer 344 rats exposed at 300 ppm for 4 h showed focal areas of red atelectasis and patchy alveolar edema with perivascular and peribronchial interstitial edema (Green et al. 1991). To assess ocular toxicity, Fischer 344 rats were exposed at 400 ppm for 4 h or 1,500 ppm for 4 min (Lefebvre et al. 1991). There was a

TABLE 7-4 Experimental Animal Toxicity Data, Exposure to Hydrogen Sulfide

Species	Exposure Route	Exposure Concentration/ Dose	Exposure Duration	Effects	NOAEL, LOAEL	Reference
ACUTE EXPOSURE (LETHALITY)						
Rat (Wistar) 5 of each sex	Inhalation	"varying concentrations"	10, 30, or 50 min	LC_{50}: 10 min = 835 ppm, 30 min = 726 ppm, 50 min = 683 ppm		Zwart et al. 1990; Arts et al. 1989
Rat (Sprague-Dawley) 5 of each sex	Inhalation	0-600 ppm	4 h	LC_{50} = 444 ppm		Tansy et al. 1981
Rat (Long Evans, Sprague-Dawley, Fischer 344) both sexes	Inhalation	"varying concentrations"	2, 4, or 6 h	LC_{50}: 2 h = 587 ppm, 4 h = 501 ppm, 6 h = 335 ppm; no strain differences were observed		Prior et al. 1988
Rat (Sprague-Dawley) males in groups of 5	Inhalation	0 or 1,655.4 ± 390.9 ppm	3 min	All treated animals died within 3 min; pulmonary edema was observed in exposed rats at necropsy		Lopez et al. 1989
Rat (Fischer 344) males	Inhalation	400-700 ppm	4 h	All animals exposed at 500-700 ppm died, animals exposed at 400 ppm did not die		Khan et al. 1990; Lopez et al. 1987, 1988a,b

Species	Exposure Route	Exposure Concentration/ Dose	Exposure Duration	Effects	NOAEL, LOAEL	Reference
Rat (Wistar) 10 males	Inhalation	800 ppm	12 min	All animals died		Beck et al. 1979
Rat (Wistar) males	Inhalation	500 ppm	2 h	No animals died		Higuchi 1977
Mouse (Swiss) 5 of each sex	Inhalation	"varying concentrations"	10, 30, or 50 min	LC_{50}: 10 min = 1160 ppm, 30 min = 800 ppm, 50 min = 676 ppm		Zwart et al. 1990; Arts et al. 1989
Mouse (CB-20) 30 females	Inhalation	100 ppm	2 h	No animals died		Elovaara et al. 1978
Mouse (NMRI) 20 female	Inhalation	100 ppm	1-4 d	No animals died		Savolainen et al. 1980
Mouse (CD1) females, 6 per group	Inhalation	722 or 1,872 ppm	50 or 10 min	All animals exposed to 722 ppm for 50 min or 1,872 ppm for 10 min died		Smith and Gosselin 1964
Rabbit (Japanese White) 5 animals	Inhalation	500-1,000 ppm	30 min	All animals died		Kage et al. 1992
Monkey (rhesus)	Inhalation	500 ppm	22 or 35 min	Animals exposed for 22 min showed ataxia, anorexia, and parenchymal		Lund and Wieland 1966

				necrosis in the brain; animals exposed for 35 min showed conjunctival irritation, sudden loss of consciousness, and respiratory and cardiac arrest		
Monkey (rhesus)	Inhalation	500 ppm	25 min, followed by 17 min exposure 3 d later	Animals showed extensive changes in gray matter and moderate liver hyperemia upon necropsy		Lund and Wieland 1966
ACUTE EXPOSURE (NONLETHAL TOXICITY)						
Rat (Fischer 344) males in groups of 12	Inhalation	0, 10, 200, or 400 ppm	4 h	All animals survived treatment; after exposure animals in 400 ppm group were lethargic but rapidly recovered; effects observed in animals exposed at 400 ppm: increased lactate dehydrogenase and protein in nasal passages (returned to basal levels 20 h after exposure), decreased bronchoalveolar cell counts, increased (up to 90%) alkaline phosphatase and lactate dehydrogenase activities in lung lavage fluid, increased (3,000%) lung protein concentrations which remained elevated 44 h after exposure, presence of nasal cavity lesions; at 200 ppm, increased lactate dehydrogenase activities in lung lavage fluid; at 10 ppm, increased cellularity	LOAEL = 10 ppm	Lopez et al. 1987, 1988a,b

Species	Exposure Route	Exposure Concentration/ Dose	Exposure Duration	Effects	NOAEL, LOAEL	Reference
				in nasal lavage fluid; necrosis and exfoliation of respiratory and olfactory mucosal cells were observed; squamous epithelial cells not affected; injured respiratory mucosa undergoing repair at 44 h; olfactory mucosa still exfoliating after 44 h		
Rat (Fischer 344) males in groups of 6	Inhalation	0, 200, or 300 ppm	4 h	Animals sacrificed 1 h after exposure; at 200 ppm: no adverse clinical signs or gross lung pathology, significant ($p<0.001$) increase in protein and lactate dehydrogenase in lavage fluid, presence of focal areas of perivascular edema and occasional collections of proteinaceous material in the alveoli compared to controls; at 300 ppm: animals were visibly stressed during exposure, lungs showed focal areas of red atelectasis and patchy alveolar edema with perivascular and peribronchial interstitial edema, significant ($p<0.001$) increased protein concentration and lactate dehydrogenase activity found in lung lavage fluid, significant ($p<0.01$)	LOAEL = 200 ppm	Green et al. 1991

				increase in abnormalities of surfactant activity parameters		
Rat (Fischer 344) males in groups of 12	Inhalation	0, 10, 50, 200, 400, or 500-700 ppm	4 h	Cytochrome c oxidase activity in lung mitochondria was significantly ($p < 0.05$) decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) at 1 hr after exposure; cytochrome c oxidase activity was not affected at 10 ppm; cytochrome c oxidase activity returned to normal 24 h after exposure in 50 ppm animals, to 89% of normal 24 h after exposure in 200 ppm animals, to 70% of normal 48 h after exposure in 400 ppm animals; cytochrome c oxidase activity had > 90% inhibition in 500-700 ppm animals (all animals died from exposure); succinate oxidase was significantly ($p<0.001$) decreased at 200 ppm (40%) and 400 ppm (63%) at 1 h after exposure; succinate-cytochrome c reductase and NADH-cytochrome c reductase were unaffected by exposure	NOAEL = 10 ppm; LOAEL = 200 ppm	Khan et al. 1990
Rat (Fischer 344) males in groups of six	Inhalation	0, 50, 200, or 400 ppm	4 h	Animals were sacrificed immediately after exposure and their lungs were lavaged; cell (>90% pulmonary alveolar macrophages) viability was significantly decreased in 400 ppm	NOAEL = 50 ppm; LOAEL = 200 ppm	Kahn et al. 1991

Species	Exposure Route	Exposure Concentration/ Dose	Exposure Duration	Effects	NOAEL, LOAEL	Reference
				group, no effect on cell numbers in 50 or 200 ppm group; complete inhibition of zymosan-induced stimulation of respiratory rates of macrophages from animals exposed to 200 or 400 ppm		
Rat (Fischer 344) males, number per group not stated	Ocular/ inhalation	0 or 400 ppm 1,500 ppm	4 h 4 min	Immediately after exposure, eyes were washed with 0.4 mL of saline and fluid collected for exfoliative eye cytology; number of exfoliated cells increased in exposed animals (44 cells/μL at 400 ppm; 35 cells/μL at 1,500 ppm) compared to controls (19 cells/μL); exposure increased proportion of conjunctival to corneal epithelial cells recovered compared to controls	LOAEL = 400 ppm	Lefebvre et al. 1991
Rat (Wistar) males, number per group not stated	Inhalation	75 ppm	20-60 min	Heart rates were decreased 10-27% during exposure and up to 1 h after exposure compared to controls; slight lung congestion in exposed animals shown at necropsy	LOAEL = 75 ppm	Kohno et al. 1991

Mouse (CB-20) 30 females (exposed) 10 females (control)	Inhalation	100 ppm	2 h	Animals were sacrificed 2, 6, 24, 48, or 72 h after exposure, with i.p. injections of ^{14}C-leucine given 2 h before sacrifice; there was no difference in brain or myelin protein or RNA content between exposed and control animals; uptake of labeled leucine in brain homogenate was significantly ($p<0.05$) reduced in the brains of exposed animals at 24 and 48 h after exposure, compared to controls; there was also a decrease in acid proteinase activity through the 72 h time point	LOAEL = 100 ppm	Elovaara et al. 1978
Rabbit (mixed breed)	Inhalation	72 ppm	1.5 h	Animals showed ventricular repolarization	LOAEL = 72 ppm	Kosmider et al. 1967
Rabbit (breed not stated) males	Dermal	NR	2 h	Animals showed slate grey skin discoloration and erythema		Laug and Draize 1942
REPEATED EXPOSURE						
Rat (Sprague-Dawley) males in groups of 5	Inhalation	0, 25, 50, 75, or 100 ppm	3 h/d, 5 d	Animals had hippocampal electrodes implanted in the dentate gyrus and CA1 region to determine effect of exposure on EEG activity in the hippocampus and neocortex; total hippocampus theta activity increased in both the dentate gyrus and CA1	LOAEL = 25 ppm	Skrajny et al. 1996

Species	Exposure Route	Exposure Concentration/ Dose	Exposure Duration	Effects	NOAEL, LOAEL	Reference
				regions after exposure at 25, 50, 75, or 100 ppm; this increase was significant ($p<0.05$) on days 3, 4, and 5 after exposure; the animals exposed at 100 ppm made a complete recovery in approximately 2 wk		
Rat (Sprague-Dawley) both sexes, groups of 15	Inhalation	0, 10.1, 30.5, or 80.0 ppm	6 h/d, 5 d/wk for 90 d	All animals survived; the following clinical signs were observed: crustiness around the ear tags, crusty noses, eyes, and muzzles, red stained fur, swollen red ears, rales, lacrimation, swollen muzzles and eyes; decreased body weight gain and brain weights observed in animals (males and females) exposed at 80.0 ppm; those effects were not observed in animals exposed at 10.1 and 30.5 ppm; no treatment-related effects related to food consumption, ophthalmology, neurological function, clinical pathology, gross pathology, histopathology, or neuropathology		CIIT 1983a
Mouse (B6C3F1) both sexes,	Inhalation	0, 10.1, 30.5, or 80.0 ppm	6 h/d, 5 d/wk for 90 d	Two animals exposed at 80 ppm showed prostration and hypoactivity and had to be sacrificed; the following		CIIT 1983b

groups of 10				clinical signs were observed: alopecia, missing anterior appendage, loss of use of anterior appendage; decreased body weight gain in animals exposed at 80 ppm; two animals did not respond to artificial light stimulus; 89% of males and 78% of females exposed at 80 ppm had inflammation of the nasal mucosa in the anterior segments of the nose; no treatment-related effects related to ophthalmology, hematology, serum chemistry, or urinalysis	
Rabbit	Inhalation	72 ppm	0.5 h/d, 5 d	Animals had cardiac arrhythmia; histochemical staining of myocardial cells from exposed rabbits showed a decrease in ATP phosphohydrolase and $NADPH_2$ oxidoreductase	Kosmider et al. 1966

Abbreviations: LC_{50}, median lethal concentration; NR, not reported.

treatment-related increase in the number of exfoliated cells and in the proportion of conjunctival to corneal epithelial cells recovered. Wistar rats exposed at 75 ppm for 20–60 min showed a decrease in heart rate of 10–27% during exposure and for up to 1 h afterwards (Kohno et al. 1991). Rabbits exposed at 72 ppm for 1.5 h showed ventricular repolarization (Kosmider et al. 1967). CB-20 mice exposed at 100 ppm for 2 h exhibited changes in brain biochemistry (Elovaara et al. 1978).

Rabbits exposed dermally to an unknown concentration of hydrogen sulfide for 2 h exhibited slate-grey skin discoloration and erythema (Laug and Draize 1942).

Repeated Exposure

Studies show that repeated exposure to hydrogen sulfide affects the central nervous, respiratory, and cardiovascular systems. Sprague-Dawley rats exposed at 25–100 ppm for 3 h/d for 5 d showed changes in electroencephalogram (EEG) activity (Skrajny et al. 1996). Decreased body weight gain and decreased brain weights were observed in Sprague-Dawley rats exposed at 80 ppm for 6 h/d, 5 d/wk for 90 d; no effects were observed in rats exposed at 10.1 and 30.5 ppm (CIIT 1983a). B6C3F1 mice exposed at 80 ppm for 6 h/d, 5 d/wk for 90 d showed inflammation of the nasal mucosa in the anterior segments of the nose (CIIT 1983b). Rabbits exposed at 72 ppm for 0.5 h/d for 5 d exhibited cardiac arrthymia and a decrease in ATP phosphohydrolase and $NADPH_2$ oxidoreductase (Kosmider et al. 1966).

OTHER CONSIDERATIONS

Structure-Activity Data

Hydrogen sulfide acts in a similar manner to cyanide (Beauchamp et al. 1984). Both compounds are potent inhibitors of the cytochrome oxidase system. Like cyanide, hydrogen sulfide can inhibit other metalloproteins containing alkali metals, such as horseradish peroxidase, potato polyphenol oxidase, and catalase, although it is not known whether those enzyme inhibitions have toxicologic significance (Smith 1996). The hydrogen sulfide anion forms a complex with methemoglobin, called sulfmethemoglobin, which is analogous to cyanmethemoglobin. The dissociation constant for sulfmethemglobin is approximately 6×10^{-6}

mol per liter and the dissociation constant for cyanmethemoglobin is approximately 2×10^{-8} mol per liter (Smith 1996). Methemoglobinemia induced by nitrite (or perhaps by some other mechanism) provided unequivocal protection and had antidotal effects against sulfide poisoning in experimental animals (Smith and Gosselin 1964). Sodium nitrate also could be antidotal for hydrogen sulfide poisoning in humans (Hall and Rumack 1997; Hoidal et al. 1986). Oxygen treatment might be useful for treatment, perhaps because of nonenzymatic oxidation of cytochrome oxidase (Bitterman et al. 1986; Hall 1996). Intravenous infusion or intraperitoneal injection of sodium bicarbonate prevented hypernea, apnea, and death in rats injected with sodium hydrogen sulfide (Almeida and Guidotti 1999). One report indicates that ethanol could lower the threshold for a person to become overcome by hydrogen sulfide exposure, although the exposure concentrations were not reported (Poda 1966).

NAVY'S RECOMMENDED SEALS

The Navy proposes to set a SEAL 1 of 10 ppm and a SEAL 2 of 20 ppm for hydrogen sulfide. These levels are based on eye irritation reported at concentrations ranging from 5 to 30 ppm, particularly with coexposure to other chemicals or eye irritants that could lower the threshold for irritation. The Navy notes that evacuation should be considered if eye irritation becomes unbearable at hydrogen sulfide concentrations between SEAL 1 and SEAL 2, and that continued exposure could result in more permanent ocular changes, including keratoconjunctivitis and vesiculation of the corneal epithelium.

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

Recommended exposure guidance levels for hydrogen sulfide from other organizations are summarized in Table 7–5. The 24-h emergency exposure guidance level (EEGL) is the most relevant guidance level to compare to the SEALs (NRC 1985). EEGLs were developed for healthy military personnel for emergency situations. An important difference between EEGLs and SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for EEGLs. Therefore, the SEALs are higher than the corresponding EEGLs.

TABLE 7–5 Recommendations from Other Organizations for Hydrogen Sulfide

Organization	Types of Exposure Level	Recommended Exposure Level	Reference
ACGIH	TLV-TWA	10 ppm (14 mg/m^3)	ACGIH 2001
ACGIH	TLV-STEL	15 ppm (21 mg/m^3)	ACGIH 2001
AIHA	ERPG 1	0.1 ppm (0.14 mg/m^3)	AIHA 2001
	ERPG 2	30 ppm (42 mg/m^3)	
	ERPG 3	100 ppm (140 mg/m^3)	
DFG	MAK (8 h/d during 40-h workweek)	10 ppm	DFG 1997
	Peak limit (10 min maximum duration)	20 ppm	
NAC	Proposed AEGL-1	0.11 ppm	Federal Register, March 15, 2000, 65(51):14185–14197.
	Proposed AEGL-2	17 ppm	
	Proposed AEGL-3	31 ppm	
NIOSH	IDLH	100 ppm (140 mg/m^3)	Ludwig et al. 1994
NIOSH	10-min ceiling	10 ppm (14 mg/m^3)	Ludwig et al. 1994
NRC	EEGL:		NRC 1985
	10 min	50 ppm (70 mg/m^3)	
	24 h	10 ppm (14 mg/m^3)	
	CEGL (90 d)	1 ppm	
OSHA	Acceptable ceiling concentration	20 ppm (28 mg/m^3)	OSHA 1997[a]

OSHA	Acceptable maximum peak, 10 min, 1 exposure for an 8-hourshift	50 ppm (70 mg/m^3)	OSHA 1997

[a]Occupational Safety and Health Standards. Code of Federal Regulations. Part 1910.1000 Air Contaminants.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AEGL, acute exposure guideline level; AIHA, American Industrial Hygiene Association; CEGL, continuous exposure guidance level; DFG, Deutsche Forschungsgemeinschaft; EEGL, emergency exposure guidance levels; ERPG, emergency response planning guideline; IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; NAC, National Advisory Committee; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; ppm; TLV-STEL, Threshold Limit Value—short-term exposure limit; TLV-TWA, Threshold Limit Value—time weighted average.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 for hydrogen sulfide of 10 ppm is too conservative. The subcommittee recommends a SEAL 1 of 15 ppm. The primary effect of concern for the crew of a disabled submarine is ocular toxicity sufficient to impair crew members' ability to escape and cause permanent eye damage. Studies with exercising healthy volunteers have shown that inhalation by mouth breathing at a concentration of 10 ppm for up to 1 h can be tolerated without significant respiratory or systemic health effects (Bhambhani et al. 1996b, 1997). Most crew members in a disabled submarine would be resting or engaged in tasks requiring light- to moderate-physical activity and would not be engaged in heavy physical activity. Serious eye effects are noted by several investigators to occur at 50 ppm and above. A summary by Guidotti (1994) noted that eye damage may occur at a concentration of 20 ppm after several days of exposure. ACGIH (1991) noted ocular toxicity may occur at 5–30 ppm; however, there were concomitant exposures to carbon disulfide or other irritant gases for toxicity occurring below 20 ppm. Based on the studies described above (e.g., Bhambhani et al. 1996b, 1997; Guidotti 1994; ACGIH 1991), the subcommittee concludes that exposure of healthy submariners to hydrogen sulfide at a concentration of 15 ppm for up to 10 d will not result in irreversible health effects or compromise their ability to escape. The subcommittee's recommended SEAL 1 of 15 ppm is further supported by studies in which rats and mice exposed at 10.1 and 30.5 ppm, 6 h/d, 5 d/wk for 90 d did not show ocular toxicity (CIIT 1983a,b).

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 20 ppm for hydrogen sulfide is too conservative. The subcommittee recommends a SEAL 2 of 30 ppm for hydrogen sulfide. Serious damage to the eye and impairment of sight are also the effects of concern for SEAL 2. The subcommittee's recommended SEAL 2 is also based on studies such as Bhambhani et al. (1996b, 1997); Guidotti (1994); and ACGIH (1991) described above for the derivation of SEAL 1. The subcommittee concludes that exposure to hydrogen sulfide at a concentration of 30 ppm for up to 24 h will not cause irreversible health effects, although it may lead to moderate eye irritation.

Pulmonary edema or sufficient inhibition of cytochrome oxidase to impair the ability to escape is not likely to be a concern until hydrogen sulfide concentrations exceed 200 ppm. Given the steep dose-response curve for respiratory paralysis and unconsciousness by hydrogen sulfide at higher concentrations, the percent inhibition is likely to be relatively low, below 50 ppm, but should increase much more rapidly at higher concentrations (e.g., above 100 ppm) (Guidotti 1996).

DATA GAPS AND RESEARCH NEEDS

Research should be conducted in experimental animals to determine the lowest concentration that causes serious effects, such as severe eye irritation or damage. Data are limited on the exposure that result in eye irritation, particularly for the concentrations, conditions, and durations associated with the transition from irritation to irreversible eye damage. More data quantifying the effects of other chemicals in lowering the threshold for ocular toxicity also are needed. Research should also be conducted to elucidate the dose-response curve for cytochrome oxidase inhibition with increasing hydrogen sulfide concentrations (i.e., 15 ppm and above).

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Hydrogen sulfide. Pp. 786–788 in Documentation of the Threshold Limit Values and Biological Exposure Indices. Vol. II, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

[ACGIH (American Conference of Governmental Industrial Hygienists). 1998. Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Threshold Limit Values for Chemical Substances and Physical Agents. Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Almeida, A.F., and T.L.Guidotti. 1999. Differential sensitivity of lung and brain to sulfide exposure: A peripheral mechanism for apnea. Toxicol. Sci. 50(2):287–293.

Ammann, H.M. 1986. A new look at physiological respiratory response to hydrogen sulfide poisoning. J. Hazard. Mater. 13(3):369–374.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological

Profile for Hydrogen Sulfide. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

Arts, J.H.E., A.Zwart, E.D.Schoen, and J.M.Klokman-Houweling. 1989. Determination of concentration-time-mortality relationships versus LC50s according to OECD guideline 403. Exp. Pathol. 37(1–4):62–66.

Beauchamp, Jr., R.O., J.S.Bus, J.A.Popp, C.J.Boreiko, and D.A.Andjelkovich. 1984. Critical review of the literature on hydrogen sulfide toxicity. Crit. Rev. Toxicol. 13(1):25–97.

Beck, J.F., F.Cormier, and J.C.Donini. 1979. The combined toxicity of ethanol and hydrogen sulfide. Toxicol. Lett. 3:311–313.

Bhambhani, Y., and M.Singh. 1991. Physiological effects of hydrogen sulfide inhalation during exercise in healthy men. J. Appl. Physiol. 71(5):1872–1877.

Bhambhani, Y., R.Burnham, G.Syndmiller, I.MacLean, and T.Martin. 1994. Comparative physiological responses of exercising men and women to 5 ppm hydrogen sulfide exposure. Am. Ind. Hyg. Assoc. J. 55(11):1030–1035.

Bhambhani, Y., R.Burnham, G.Syndmiller, I.MacLean, and T.Martin. 1996a. Effects of 5 ppm hydrogen sulfide inhalation on biochemical properties of skeletal muscle in exercising men and women. Am Ind. Hyg. Assoc. J. 57(5):464–468.

Bhambhani, Y., R.Burnham, G.Syndmiller, I.MacLean, and R.Lovlin. 1996b. Effects of 10 ppm hydrogen sulfide inhalation on pulmonary function in healthy men and women. J. Occup. Environ. Med. 38 (10):1012–1017.

Bhambhani, Y., R.Burnham, G.Syndmiller, and I.MacLean. 1997. Effects of 10 ppm hydrogen sulfide inhalation in exercising men and women. Cardiovascular, metabolic, and biochemical responses. J. Occup. Environ. Med. 39(2):122–129.

Bitterman, N., Y.Talmi, A.Lerman, Y.Melamed, and U.Taitelman. 1986. The effect of hyperbaric oxygen on acute experiemental sulfide poisoning in the rat. Toxicol. Appl. Pharmacol. 84 (2):325–328.

Breysse, P.A. 1961. Hydrogen sulfide fatality in a poultry feather fertilizer plant. Am. Ind. Hyg. Assoc. J. 22:220–222.

CIIT (Chemical Industry Institute of Toxicology). 1983a. 90-Day Vapor Inhalation Study of Hydrogen Sulfide in Sprague-Dawley Rats. Report to the Chemical Industry Institute of Toxicology, Research Triangle Park, NC, by ToxiGenics, Inc. CIIT docket #32063.

CIIT (Chemical Industry Institute of Toxicology). 1983b. 90-Day Vapor Inhalation Study of Hydrogen Sulfide in B6C3F1 Mice. Report to the Chemical Industry Institute of Toxicology, Research Triangle Park, NC, by ToxiGenics, Inc. CIIT docket #42063.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, 1st Ed. Report No. 33. Weinheim: Wiley-VCH.

Donham, K.J., D.C.Zavala, and J.Merchant. 1984. Acute effects of the work environment on pulmonary functions of swine confinement workers. Am. J. Ind. Med. 5(5):367–376.

Elovaara, E., A.Tossavainen, and H.Savolainen. 1978. Effects of subclinical hydrogen sulfide intoxication on mouse brain protein metabolism. Exp. Neurol. 62(1):93–98.

Fuller, D.C., and A.J.Suruda. 2000. Ocupationally related hydrogen sulfide deaths in the United States from 1984 to 1994. J. Occup. Environ. Med. 42(9):939–942.

Green, F.H.Y., S.Schurch, G.T.De Sanctis, J.A.Wallace, S.Cheng, and M.Prior. 1991. Effects of hydrogen sulfide exposure on surface properties of lung surfactant. J. Appl. Physiol. 70 (5):1943–1949.

Guidotti, T.L. 1994. Occupational exposure to hydrogen sulfide in the sour gas industry: some unresolved issues. Int. Arch. Occup. Environ. Health 66(3):153–160.

Guidotti, T.L. 1996. Hydrogen sulphide. Occup. Med. (Lond) 46(5):367–371.

Hall, A.H. 1996. Systemic asphyxiants. Pp. 1706–1718 in Intensive Care Medicine, 3rd Ed., J.M.Rippe, R.S.Irwin, M.P.Fink, and R.B.Cerra, eds. Boston, MA: Little Brown.

Hall, A.H., and B.H.Rumack 1997. Hydrogen sulfide poisoning: An antidotal role for sodium nitrite. Vet. Hum. Toxicol. 39(3):152–154.

Hessel, P.A., F.A.Herbert, L.S.Melenka, K.Yoshida, and M.Nakaza. 1997. Lung health in relation to hydrogen sulfide exposure in oil and gas workers in Alberta, Canada. Am. J. Ind. Med. 31 (5):554–557.

Higuchi, Y. 1977. Behavioral studies on toxicity of hydrogen sulfide by means of conditioned avoidance responses in rats, [in Japanese]. Nippon Yakurigaku Zasshi 73(3):307–319.

Hoidal, C.R., A.H.Hall, M.D.Robinson, K.Kulig, and B.H.Rumack 1986. Hydrogen sulfide poisoning from toxic inhalations of roofing asphalt fumes. Ann. Emerg. Med. 15(7):826–830.

Hsu, P., H.W.Li, and Y.T.Lin. 1987. Acute hydrogen sulfide poisoning treated with hyperbaric oxygen. J. Hyperbaric Med. 2(4):215–221.

Jaakkola, J.J., V.Vikka, O.Marttila, P.Jäppinen, and T.Haahtela. 1990. The South Karelia air pollution study. The effects of malodorous sulfur compounds from pulp mill on respiratory and other symptoms. Am. Rev. Respir. Dis. 142(6 Pt 1):1344– 1350.

Jäppinen, P., V.Vikka, O.Marttila, and T.Haahtela. 1990. Exposure to hydrogen sulfide and respiratory function. Br. J. Ind. Med. 47(12):824–828.

Kage, S., T.Nagata, K.Kimura, K.Kudo, and T.Imamura. 1992. Usefulness of thiosulfate as an indicator of hydrogen sulfide poisoning in forensic toxicological examination: A study with animal experiments. Jap. J. Forensic Toxicol. 10(3):223– 227.

Kangas, J., and H.Savolainen. 1987. Urinary thiosulfate as an indicator of exposure to hydrogen sulphide vapour. Clin. Chim. Acta 164(1):7–10.

Khan, A.A., M.M.Schuler, M.G.Prior, S.Yong, R.W.Coppock, L.Z.Florence, and L.E. Lillie. 1990. Effects of hydrogen sulfide exposure on lung mitochondrial respiratory chain enzymes in rats. Toxicol. Appl. Pharmacol. 103(3):482–490.

Khan, A.A., S.Yong, M.G.Prior, and L.E.Lillie. 1991. Cytotoxic effects of hydrogen sulfide on pulmonary alveolar macrophages in rats. J. Toxicol. Environ. Health 33(1):57–64.

Kimura, K., M.Hasegawa, K.Matsubara, C.Maseda, M.Kagawa, S.Takahashi, and K. Tanabe. 1994. A fatal disaster case based on exposure to hydrogen sulfide—an

estimation of the hydrogen sulfide concentration at the scene. Forensic Sci. Int. 66(2):111–116.

Kohno, M., E.Tanaka, T.Nakamura, T.Nakamura, N.Shimojo, and S.Misawa. 1991. Influence of the short-term inhalation of hydrogen sulfide in rats. Eisei Kagaku. 37(2):103–106.

Kosmider, S., E.Rogala, and A.Pacholek 1967. Electrocardiographic and histochemical studies of the heart muscle in acute experimental hydrogen sulfide poisoning. Arch. Immunol. Ther. Exp. 15(5):731–740.

Kosmider, S., E.Rogala, and A.Pacholek 1966. Studies on the toxic mechanism of effect of hydrogen sulfide. [in German]. Int. Arch. Gewerbepathol. Gewerbehyg. 22(1):60–76.

Laug, E.P., and J.H.Draize. 1942. The percutaneous absorption of ammonia hydrogen sulfide and hydrogen sulfide. J. Pharmacol. Exp. Ther. 76:179–188.

Lefebvre, M., D.Yee, D.Fritz, and M.G.Prior. 1991. Objective measures of ocular irritation as a consequence of hydrogen sulphide exposure. Vet. Hum. Toxicol. 33(6):564–566.

Lide, D.R., ed. 1991. CRC Handbook of Chemistry and Physics, 72nd Ed. Boca Raton: CRC.

Lopez, A., M.Prior, S.Yong, M.Albassam, and L.E.Lillie. 1987. Biochemical and cytological alterations in the respiratory tract of rats exposed for 4 hours to hydrogen sulfide . Fundam. Appl. Toxicol. 9(4):753–762.

Lopez, A., M.Prior, L.E.Lillie, C.Gulayets, and O.S.Atwal. 1988a. Histologic and ultrastructural alterations in lungs of rats exposed to sub-lethal concentrations of hydrogen sulfide. Vet. Pathol. 25(5):376–384.

Lopez, A., M.Prior, S.Yong, L.Lillie, and M.Lefebvre. 1988b. Nasal lesions in rats exposed to hydrogen sulfide for four hours. Am. J. Vet. Res. 49(7):1107–1111.

Lopez, A., M.G.Prior, R.J.Reiffenstein, and L.R.Goodwin. 1989. Peracute toxic effects of inhaled hydrogen sulfide and injected sodium hydrosulfide on the lungs of rats. Fundam. Appl. Toxicol. 12(2):367–373.

Ludwig, H.R., S.G.Cairell, and J.J.Whalen. 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHS). Cincinnati, OH: National Institute for Occupational Safety and Health. PB 94–195047, National Technical Information Service, Springfield, VA.

Lund, O.E. and H.Wieland. 1966. Pathologic-anatomic findings in experimental hydrogen sulfide poisoning (H2S). [in German]. Int. Arch. Arbeitsmed. 22(1):46–54.

Marttila, O., J.J.Jaakkola, K.Partti-Pellinen, V.Vilkka, and T.Haahtela. 1995. South Karelia air pollution study: Daily symptom intensity in relation to exposure levels of malodorous sulfur compounds from pulp mills. Environ. Res. 71(2):122–127.

Milby, T.H. 1962. Hydrogen sulfide indoxication. J. Occup. Med. 4(8):431–437.

Milby, T.H., and R.C.Baselt. 1999. Health hazards of hydrogen sulfide: Current status and future directions. Environ. Epidemiol. Toxicol. 1(3/4):262–269.

Morse, D.L., M.A.Woodbury, and K.Rentmeester. 1981. Death caused by fermenting manure. JAMA 245(1):63–64.

Nagata, T., S.Kage, K.Kimura, K.Kudo, and M.Noda. 1990. Sulfide concentrations in postmortem mammalian tissues. J. Forensic Sci. 35(3):706–712.

Nesswetha, W. 1969. Eye lesions caused by sulphur compounds. [in German]. Arbeitsmed. Sozialmed. Arbeitshyg. 4:288–290.

NIOSH (National Institute of Occupational Safety and Health). 1991. Fatal Accident Circumstances and Epidemiology (FACE) Report: Two Maintenance Workers Die After Inhaling Hydrogen Sulfide in Manhole, January 31, 1989. Morgantown, WV. NTIS PB91212761.

NRC (National Research Council). 1985. Hydrogen sulfide. Pp. 55–68 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

Osbern, L.N., and R.O.Crapo. 1981. Dung lung: A report of toxic exposure to liquid manure. Ann. Intern. Med. 95(3):312–314.

Partti-Pellinen, K., O.Martilla, V.Vilkka, J.J.Jaakkola, P.Jäppinen, and T.Haahtela. 1996. The South Karelia air pollution study: Effects of low-level exposure to malodorous sulfur compounds on symptoms. Arch. Environ. Health 51(4):315–320.

Poda, G.A. 1966. Hydrogen sulfide can be handled safely. Arch. Environ. Health 12(6):795–800.

Prior, M.G., A.K.Sharma, S.Young, and A.Lopez. 1988. Concentration-time interactions in hydrogen sulfide toxicity in rats. Can. J. Vet. Res. 52(3):375–379.

Reiffenstein, R.J., W.C.Hulbert, and S.H.Roth. 1992. Toxicology of hydrogen sulfide. Annu. Rev. Pharmacol. Toxicol. 32:109–134.

Richardson, D.B. 1995. Respiratory effects of chronic hydrogen sulfide exposure. Am. J. Ind. Med. 28(1):99–108.

Ronk, R., and M.K.White. 1985. Hydrogen sulfide and the probabilities of “inhalation” through a tympanic membrane defect. J. Occup. Med. 27(5):337–340.

Savolainen, H., R.Tenhunen, E.Elovaara, and A.Tossavainen. 1980. Cumulative biochemical effects of repeated subclinical hydrogen sulfide intoxication in mouse brain. Int. Arch. Occup. Environ. Health 46(1):87–92.

Skrajny, B., R.J.Reiffenstein, R.S.Sainsbury, and S.H.Roth. 1996. Effects of repeated exposures of hydrogen sulfide on rat hippocampal EEG. Toxicol. Lett. 84(1):43–53.

Smith, R.P. 1996. Toxic responses of the blood. Pp. 335–354 in Casarett and Doull’s Toxicology, 5th Ed., C.Klaassen, ed. New York: McGraw Hill.

Smith, R.P., and G.E.Gosselin. 1964. The influence of methemoglobinemia on the lethality of some toxic anions: II. Sulfide. Toxicol. Appl. Pharmacol. 6:584–592.

Snyder, J.W., E.F.Safir, G.P.Summerville, and R.A.Middleberg. 1995. Occupational fatality and persistent neurological sequelae after mass exposure to hydrogen sulfide. Am. J. Emer. Med. 13(2):199–203.

Suarez, F.L., and M.D.Levitt. 1999. Hydrogen sulfide production and detoxification in the colon. Environ. Epidemiol. Toxicol. 1(3/4):256–261.

Tansy, M.F., F.M.Kendall, J.Fantasia, W.E.Landin, R.Oberly, and W.Sherman. 1981. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health. 8(1– 2):71–88.

Tvedt, B., K.Skyberg, O.Aaserud, A.Hobbesland, and T.Mathiesen. 1991a. Brain damage caused by hydrogen sulfide: A follow-up study of six patients. Am. J. Ind. Med. 20(1):91–101.

Tvedt, B., A.Edlund, K.Skyberg, and O.Forberg. 1991b. Delayed neuropsychiatric sequelae after acute hydrogen sulfide poisoning: Affection of motor function, memory, vision, and hearing. Acta. Neurol. Scand. 84(4):348–351.

Voigt, G.E., and P.Müller. 1955. The histochemical effect of hydrogen sulfide poisoning. [in German]. Acta Histochem 1:223–239.

Walton, D.C., and M.G.Witherspoon. 1925. Skin absorption of certain gases. J. Pharmacol. Exp. Ther. 26:315–324.

Wetterau, H., W.Oekert, and U.G.Knape. 1964. Tests for the application of dried green fodder with higher hydrogen sulfide content (experiments with poultry and fattened pigs). [in German]. Fetterung. 5:383–393.

Wever, R., B.F.Van Gelder, and D.V.Dervartanian. 1975. Biochemical and biophysical studies on cytochrome c oxidase. 10. Reaction with sulphide. Biochim. Biophys. Acta. 387(2):189–193.

WHO (World Health Organization). 1987. Hydrogen sulfide. Pp. 233–241 in Air Quality Guidelines for Europe. European Series No. 23. Copenhagen, Denmark: World Health Organization.

Winek, C.L., W.D.Collum, and C.H.Wecht. 1968. Death from hydrogen sulfide fumes. Lancet 1 (May 18):1096.

Zwart, A., J.H.E.Arts, J.M.Klokman-Houweling, and E.D.Schoen. 1990. Determination of concentration-time-mortality relationships to replace LC 50 values. Inhalation Toxicol. 2:105–117.

8

Nitrogen Dioxide

This chapter reviews the physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on nitrogen dioxide. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine from exposure to nitrogen dioxide and to evaluate submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to nitrogen dioxide.

BACKGROUND INFORMATION

Nitrogen dioxide is a reddish-brown gas that is heavier than air. It typically exists in the atmosphere as an equilibrium mixture with nitrogen tetroxide. As a relatively stable free radical, it can be found in ambient air at high concentrations near a source such as automobile exhaust or an electric arc. High concentrations are also found in grain silos. The chemical and physical properties of nitrogen dioxide are summarized in Table 8–1.

The initial combustion product of nitrogen and oxygen is nitric oxide, which on further oxidation gradually turns into nitrogen dioxide. Atmospheric concen

trations result from many natural and anthropogenic sources, including combustion of fossil fuels for heating and transportation, power generation, industrial processes, solid-waste disposal, and forest fires. In forested and rural areas of the United States, ambient nitrogen dioxide concentrations average less than 0.10 ppm (parts per million), whereas in urban areas peak levels may exceed 0.2 ppm, particularly in the late afternoon and evening (EPA 1993). As a major component of smog, nitrogen dioxide has been measured at concentrations of between 0.1 and 0.8 ppm (maximum hourly average) with short-term peaks of 1.27 ppm (Mohsenin 1994). Indoor air also can contain nitrogen dioxide at peak concentrations of 2–4 ppm as a result of the use of gas-burning appliances or kerosene heaters. Firefighters can encounter concentrations of up to 1 ppm, but rarely higher (Gold et al. 1978).

TABLE 8–1 Physical and Chemical Properties for Nitrogen Dioxide

Characteristic	Value
Molecular formula	NO_2
Molecular weight	46.01
CAS number	10102–44–0
Physical state	Gas
Color	Reddish brown
Odor	Sweet
Odor threshold	0.4 ppm (recognition)
	4.0 ppm (<100% identification)
Melting point	–9.3 °C
Boiling point	21.15°C
Solubility in water	0.037 mL/mL at 35°C
Vapor pressure	720 torr at 20°C
	800 mm Hg at 25°C
Vapor density	1.58 (air=1)
Conversion factors	1 ppm=1.88 mg/m^3
25°C, 1 atm	1 mg/m^3=0.53 ppm

Sources: EPA (1990, 1993); ACGIH (1991); Mohsenin (1994); Budavari et al. (1996).

TOXICOKINETIC CONSIDERATIONS

Nitric oxide, a precursor of nitrogen dioxide, occurs naturally in the human body, where it acts as endothelial derived relaxing factor (EDRF), a neurotransmitter, and in unidentified ways in the nose, sinuses, and lower airways. Up to 15 ppm can be found normally in the nose and sinuses (DuBois et al. 1998). The substrate is l-arginine, and the enzymes consist of different forms of nitric oxide synthase, which turn arginine into citrulline. Inhaled nitric oxide gas is used at concentrations of up to 50 ppm to decrease pulmonary arterial pressure. Nitric oxide reacts in tissues to form nitrites and nitrates.

Nitrogen dioxide is relatively insoluble; however, its reactivity is sufficient to permit chemical interaction and absorption along the entire tracheobronchial tree (NRC 1985). In humans exposed at 0.29–7.2 ppm of nitrogen dioxide for approximately 30 min during quiet respiration and during exercise, the total respiratory tract absorption was measured at 81–90% and 91–92%, respectively, in healthy adults and 72% and 87%, respectively, in people with asthma (EPA 1993). In monkeys exposed to 0.30–0.91 ppm nitrogen dioxide for less than 10 min, 50–60% of the inhaled gas was retained during quiet respiration (Goldstein et al. 1977). The nitrogen dioxide was distributed throughout the lungs. In rats, nitrogen dioxide appears to be retained mostly in the upper respiratory tract (Russell et al. 1991). Pulmonary absorption of nitrogen dioxide could be the result of the nitrate-forming reaction between the inhaled gas and the pulmonary surface lining layer (Postlethwait and Bidani 1990, 1994; Saul and Archer 1983). Uptake of nitrogen dioxide is saturable. The reaction in the lungs is not known, but could involve hydrogen abstraction by readily oxidizable tissue components, such as proteins and lipids, to form lipid peroxides, nitrous acid, and nitrite radicals (Postlethwait and Bidani 1994). Alternatively, nitrogen dioxide might react with water to form nitrous and nitric acids (Goldstein et al. 1977).

Inhaled nitrogen dioxide and its metabolites are distributed throughout the body by the blood stream (Goldstein et al. 1977). The nitrite that is formed in the lungs diffuses into the vascular space and is oxidized to nitrate in interactions with red blood cells (Postlethwait and Mustafa 1981). In mice, the half-lives of nitrite and nitrate are several minutes and 1 h, respectively, and methemoglobin is not formed by nitrogen dioxide or nitrite in vivo, although it is formed in vitro (Oda et al. 1981). Urinary excretion of nitrate has been shown to be related linearly to the nitrogen dioxide concentration administered (Saul and Archer 1983).

HUMAN TOXICITY DATA

Outdoor air pollution studies on the effects of nitrogen dioxide in healthy adult humans do not conclusively show a relationship between ambient concentrations of nitrogen dioxide and respiratory effects. However, children and people with asthma appear to be at greater risk of respiratory effects.

Reports of workers who have been exposed to high concentrations as a result of industrial processes, such as welding, show increased incidence of respiratory illness, although in most cases the effects are reversible. Symptoms of exposure to nitrogen dioxide include dyspnea, cough, pulmonary edema, and irritation of the mucous membranes (Table 8–2).

Experimental Studies

Experimental studies of nitrogen dioxide exposure at concentrations of up to 5 ppm with healthy subjects and people with asthma have shown little if any adverse health effects. Exposures up to 0.6 ppm in healthy men and women, whether at rest or during exercise, do not appear to result in decreased pulmonary function although continuous exposure at 1.5 ppm for 3 h resulted in a slight but significant fall in forced expiratory volume (FEV) and forced vital capacity (FVC) response to carbachol (Frampton et al. 1991). Studies at higher concentrations suggest that a threshold for pulmonary function effects exists at approximately 5 ppm. Changes in bronchoalveolar lavage fluid and blood have been reported after exposure of healthy adults to nitrogen dioxide, with exposure at concentrations of 1–4 ppm for up to 5 h resulting in enzyme activity alterations (Devlin et al. 1992; Goings et al. 1989; Hackney et al. 1978; Linn and Hackney 1983; Rasmussen et al. 1992).

Several studies on people with asthma showed that low concentrations (0.12– 1 ppm) did not significantly affect pulmonary function in adults or adolescents, whether they were exercising or at rest (Kleinman et al. 1983; Koenig et al 1985, 1987; Linn and Hackney 1984; Mohsenin 1987; Utell and Morrow 1989; Roger et al. 1990; Rubinstein et al. 1990; Sackner et al. 1981; Vagaggini et al. 1996). However, Kerr et al. (1978) and Bauer et al. (1985) reported that exposure at 0.5 and 0.3 ppm for 2–4 h resulted in a slight reduction in forced expiratory volume in 1 s (FEV_1) and specific airway conductance, headache, chest tightness, and wheezing. Studies on airway hyperreactivity in people with asthma also have been inconclusive and followed a pattern similar to that shown in pulmonary function studies.

TABLE 8-2 Human Toxicity Data, Exposure to Nitrogen Dioxide

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
EXPERIMENTAL STUDIES					
Healthy men and women	Inhalation	0.6 ppm	1-3 h with intermittent or continuous exercise	No effects in several studies. Continuous exposure to 1.5 ppm for 3 h resulted in slight fall in FEV_1 and FVC response to carbachol.	Folinsbee et al. 1978; Adams et al. 1987; Frampton et al. 1991; Hazucha et al. 1994
Healthy adults	Inhalation	1, 2 ,2.3 ,4, 5 ppm	1.25-5 h	No effects observed at 1-3 ppm for up to 5 h. At 4 ppm for 1.25 h, no effects with light or heavy exercise. At 5 ppm for 2 h, decreased alveolar oxygen partial pressure and increase in airway resistence in 6 of 11 subjects.	Hackney et al. 1978; Devlin et al. 1992; Goings et al. 1989; Rasmussen et al. 1992; Linn and Hackney 1983; von Nieding and Wagner 1979
Volunteers	Inhalation	30 ppm	2 h	Burning sensation in nose and chest, cough, dyspnea, sputum production.	NRC 1977
Healthy adults	Inhalation	2 ppm	4, 6 h	Influx of polymorphonuclear leukocytes in bronchoalveolar lavage fluid.	Devlin et al 1992; Frampton et al. 1992
Healthy adults	Inhalation	2.3 ppm	5 h	Decrease in serum glutathione peroxidase activity.	Rasmussen et al. 1992

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
Healthy adults	Inhalation	1-4 ppm	3 h	Decrease in red blood cell membrane acetylcholinesterase activity; increase in red blood cell lipids and glucose-6-phosphate dehydrogenase activity, higher concentration resulted in decrease in alpha-1-protease inhibitor activity but not overall enzyme activity in BALF. Mucociliary activity ceased after 45-min exposure to 1.5 and 3.5 ppm for 20 min.	Devlin et al. 1992; Frampton et al. 1992; Rasmusen et al. 1992; Posin et al. 1978; Mohsenin and Gee 1987; Helleday et al. 1995
Adults and adolescents with asthma	Inhalation	0.12-4 ppm	40 min - 4 h	No change in pulmonary function was noted in several studies of adult and adolescent, whether at rest or with intermittent exercise.	Koenig et al. 1987; Koenig et al. 1985; Kleinman et al. 1983; Rubinstein et al. 1990; Vagaggini et al. 1996; Utell and Morrow 1989; Mohsenin 1987; Roger et al. 1990; Sackner et al. 1981; Linn and Hackney 1984

13 asthma patients	Inhalation	0.5 ppm	2 h	Slight burning of eyes and headache, chest tightness or labored breathing with exercise; no change in pulmonary function.	Kerr et al. 1978
20 patients with chronic obstructive pulmonary disease	Inhalation	0.3 ppm	4 h	Reduced FEV_1 and specific airway conductance after exercise. 1 of 6 had chest tighness and wheezing.	Morrow et al. 1992
20 asthma patients	Inhalation	0.1 ppm	1 h	Increase in specific airway resistence and enhanced bronchoconstrictor effect of carbachol in 13 of 20 subjects.	Orehek et al. 1976
Asthma patients	Inhalation	0.4 ppm	1 or 6 h	Decrease in FEV_1 with challenge with house dust mite antigen after 1 h but not after 6 h when compared with nonasthma group.	Tunnicliffe et al. 1994; Devalia et al. 1994
ACCIDENTAL EXPOSURES					
4 men	Inhalation	Unknown	≤ 10 min	Headache, cough, pulmonary edema, sinusitis, upper respiratory tract irritation, fever, chest tightness, shortness of breath; dypsnea.	Tse and Bockman 1970

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
OCCUPATIONAL STUDIES					
17 grain silo workers	Inhalation	Unknown	NR	Dyspnea, cough, chest pain, eye irritation, rapid breathing, death with diffuse alveolar damage and edema.	Douglas et al. 1989
1 worker	Inhalation	At least 90 ppm (acetylene torch)	30 min	Shortness of breath, pulmonary edema.	Norwood et al. 1966
Welders	Inhalation	30 ppm	40 min	Dyspnea, cough, headache, tightness or pain in chest, nausea, cyanosis, viral pneumonia, pulmonary edema.	Morley and Silk 1970
Diesel bus garage workers	Inhalation	≥ 0.3 ppm	NR	Cough, itching, burning or watering eyes, difficult breathing, chest tightness, and wheeze but no reduction in pulmonary function.	Gamble et al. 1987
Traffic officers	Inhalation	0.045-0.06 ppm	NR	Slight increase in bronchitis and colds compared with officers in low traffic area.	Speizer and Ferris 1973

EPIDEMIOLOGY STUDIES					
Children and families living near TNT (trinitro-toluene) plant	Inhalation	0.083 ppm (average 24-h concentration)	Several years	Respiratory illness rates were consistently higher and lower $FEV_{0.75}$ for people with higher exposures. Follow-up several years later found similar results. Reanalysis of data found inverse relationship between illness and nitrogen dioxide concentration in several subpopulations.	Shy et al. 1970a,b; Love et al. 1982; Harrington and Krupnick 1985
Children	Inhalation	≥ 80 ppb hourly peak levels	NR	Increased occurrence of sore throats, colds and school absences in children exposed to unflued gas heating in classrooms.	Pilotto et al. 1997
Adult asthma patients	Inhalation	>0.3 ppm	Cooking on gas stove	Slight decreases in FEV_1 and peak expiratory flow.	Goldstein et al. 1988

Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NR, not reported.

Accidental Exposures

Death from accidental exposure to nitrogen dioxide occurs at concentrations generally greater than 150 ppm for healthy adults. Survivable exposures of brief duration at high concentrations of nitrogen dioxide have occurred from combustion of cordite in military vehicles (Elsayed 1994).

Occupational Studies

Silo filler's disease is associated with the accumulation of nitrogen dioxide in grain silos that can reach concentrations of 200–4,000 ppm within 2 d. Respiratory effects among workers have been reported in the literature as far back as the 1950s (Grayson 1956; Lowry and Schuman 1956). In a report of 17 silo workers, 16 had dyspnea, cough, chest pain, eye irritation, and rapid breathing; one worker died with diffuse alveolar damage and pulmonary edema; and one worker developed bronchiolitis fibrosa obliterans years later (Grayson 1956; Lowry and Schuman 1956; Milne 1969).

Other occupations, such as welding with an acetylene torch, also have been found to result in exposure to nitrogen dioxide. Although most reports indicate that symptoms, such as dyspnea, cough, headache, chest pain and tightness, and cyanosis, are transient and respond to oxygen and antibiotic treatment, one welder died from viral pneumonia 43 d after exposure (Morley and Silk 1970). Concentrations might have been as high as 30 ppm for 40 min but not all welders were affected.

Epidemiologic Studies

Numerous reviews published since 1970 have examined the effects of nitrogen dioxide on humans; however, the evidence of adverse health effects from the studies cited in the reviews is inconclusive. EPA (1993) reviewed more than 20 studies on the epidemiology of nitrogen dioxide and other nitrogen oxides. In general studies showed that infants and children appear to have increased respiratory symptoms as a result of increased exposure to nitrogen dioxide, but a quantitative relationship could not be established. Studies that attempted to show a causal relationship between indoor and outdoor nitrogen dioxide exposure and long-term changes in pulmonary function were marginally significant. No studies were found that assessed short-term exposures for indoor nitrogen dioxide.

In a meta-analysis of the epidemiologic studies, EPA reported a 20% increase in the odds of respiratory illness in children exposed long-term to a nitrogen dioxide concentration of 0.01 ppm (Hasselblad et al. 1992).

EXPERIMENTAL ANIMAL TOXICITY DATA

The primary target of nitrogen dioxide is the lung, although it can produce changes in the blood and other organs as well (EPA 1993). Numerous studies have been conducted to assess the toxicity of exposure to nitrogen dioxide in experimental animals. Many of them are summarized below and in Table 8–3. A review of the data also is available in the *Air Quality Criteria for Oxides of Nitrogen,* Volume III (EPA 1993) and in the *Emergency Exposure Guidance Levels,* Volume 4 (NRC 1985).

Acute Exposure

For 5- to 60-min exposures, rat LC_{50} (the concentration that is lethal to 50% of test animals) range from 416 to 115 ppm in one study (Carson et al. 1962) and from 833 to 168 ppm in another study (Gray et al. 1954). A 15-min LC_{50} value for rabbits is 315 ppm (Carson et al. 1962). Hine et al. (1970) exposed rats, mice, dogs, rabbits, and guinea pigs to various concentrations of nitrogen dioxide. No mortality occurred up to 40 ppm. The first deaths were observed in rats and mice exposed at 50 ppm for 24 h, in dogs exposed at 76 ppm for 4 h, in rabbits exposed at 75 ppm for 1 h, and in guinea pigs exposed at 50 ppm for 1 h. Histologic signs in all species included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and edema (Hine et al. 1970). Additional studies in rats, mice, monkeys, and dogs show that exposure to nitrogen dioxide causes pulmonary edema (e.g., alveolar and interstital edema) and histological changes (e.g., bronchiolitis, bronchiolar epithelial cell hyperplasia, loss of cells, necrosis of type I cells, and type II cell hyperplasia) (Carson et al. 1962; Dowell et al. 1971; Hayashi et al. 1987; Henry et al. 1969; Goldstein et al. 1973; Guth and Mavis 1985; Lehnert et al. 1994; Siegel et al. 1989; Stavert and Lehnert 1990; Stephens et al. 1972; Suzuki et al. 1982). In animals that did not die, the histopathologic changes were reversible, and the animals healed after a time. Enhanced susceptibility to infection was observed in mice exposed at 5 ppm for 6 h/d for 2 d (Rose et al. 1989) and in monkeys exposed at 50 ppm for 2 h (Henry et al. 1969).

TABLE 8-3 Experimental Animal Toxicity Data, Exposure to Nitrogen Dioxide

Species	Route	Concentration (ppm)	Duration	Effect	Reference
ACUTE TOXICITY (LETHALITY)					
Rat	Inhalation	416 ppm	5 min	LC_{50}; clinical signs included severe respiratory distress, eye irritation, 10-15% decrease in body weight; pathology showed darkened areas on surface of lung.	Carson et al. 1962
Rat	Inhalation	201 ppm	15 min	LC_{50}; clinical signs included severe respiratory distress, eye irritation, 10-15% decrease in body weight; pathology showed darkened areas on surface of lung.	Carson et al. 1962
Rat	Inhalation	162 ppm	30 min	LC_{50}; clinical signs included severe respiratory distress, eye irritation, 10-15% decrease in body weight; pathology showed darkened areas on surface of lung.	Carson et al. 1962
Rat	Inhalation	115 ppm	60 min	LC_{50}; clinical signs included severe respiratory distress, eye irritation, 10-15% decrease in body weight; pathology showed darkened areas on surface of lung.	Carson et al. 1962
Rat	Inhalation	88-1,445 ppm	2-240 min	LC_{50} values for males (200-300 g): 1,445 for 2 min, 833 ppm for 5 min, 420 ppm for 15 min, 174 for 30 min, 168 ppm for 60 min, and 88 ppm for 240 min. Deaths attributable to pulmonary edema.	Gray et al. 1954

Rat	Inhalation	25, 75, 125, 175, 200 ppm	10 min	No signs of toxicity at 25 ppm; at ≥75 ppm rats had dose-related increases in lung weight, subpleural hemorrhage, pale discoloration of lung, atypical pneumonia, edema, focal desquamation of the terminal bronchiolar epithelium, increased macrophages and neutrophilic leucocytes, and interstitial thickening of centriacinar speta (175 and 200 ppm only). Stertorous respirations were heard in animals exposed to 175 and 200 ppm. 1 of 6 and 1 of 9 rats died at two highest doses, respectively.	Meulenbelt et al. 1992a,b
Rat	Inhalation	175 ppm; 400 ppm	10, 20, 30 min; 5, 10, 20 min	All animals had stertorous respirations and lung weights were increased. At 175 ppm, 5 of 6 rats died at 20- and 30-min exposure groups. At 400 ppm, all 6 rats died in 10- and 20-min groups. Histology revealed foamy, serosanguinous fluid in trachea, subpleural bleeding, pale discoloration.	Meulenbelt et al. 1992a,b
Rat	Inhalation	5-250 ppm	30 min-24 h	At concentrations greater >40 ppm lacrimation, reddening of conjunctivae, and increased respiration noted. Mortality at 50 ppm after 24 h with gasping and lung edema. Histologic signs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, edema.	Hine et al. 1970

Species	Route	Concentration	Duration	Effect	Reference
Mouse	Inhalation	5, 20, 40 ppm	12 h	At two highest doses, body weight decreased.	Hidekazu and Fujio 1981
Mouse	Inhalation	5-250 ppm	30 min-24 h	At concentrations >40 ppm lacrimation, reddening of conjunctivae, increased respiration noted. Mortality occurred at 50 ppm after 24 h, with gasping and lung edema. Histologic signs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, edema.	Hine et al. 1970
Dog	Inhalation	1,000 ppm 5,000 ppm 20,000 ppm	136 min 5-45 min 15 min	At 5,000 ppm for 35-45 min and at 20,000 ppm all dogs died due to pulmonary edema. One dog at 20,000 ppm had cyanosis attributable to methemoglobin formation.	Greenbaum et al. 1967
Dog	Inhalation	5-250 ppm	30 min-24 h	At concentrations >40 ppm lacrimation, reddening of conjunctivae, increased respiration noted. Mortality occurred at 75 ppm after 4 h with gasping and lung edema. Histologic signs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, edema.	Hine et al. 1970
Rabbit	Inhalation	315 ppm	15 min	LC_{50}; clinical signs of toxicity including severe respiratory distress, eye irritation, body weight decrease, and death at 30 min to 3 d. Pathology showed darkened areas on lung surface.	Carson et al. 1962

Rabbit	Inhalation	5-250 ppm	30 min-24 h	At concentrations >40 ppm lacrimation, reddening of conjunctivae, increased respiration noted. Mortality occurred at 75 ppm at 60 min with gasping and lung edema. Histologic signs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, edema.	Hine et al. 1970
Rabbit	Inhalation	125, 175, 250, 400, 600, 800 ppm	10 min	2 of 3 animals at 800 ppm died 7-21 h after exposure. At 250 ppm and greater, lung weights were higher and lung homogenates contained increased protein, LDH, glutathione peroxidase, and glucose-6-phosphate dehydrogenase. At ≥175 ppm, BAL also had increased protein, albumin, LDH, and angiotensin-converting enzyme activities and all exposed animals had increased neutrophilic leucocytes. Dose-related increases in pneumonitis, macrophage influx. Edema occurred at ≥250 ppm, hemorrhaging at ≥400 ppm, and desquamation of bronchiolar epithelium at ≥600 ppm.	Meulenbelt et al. 1994
Guinea pig	Inhalation	5-200 ppm	30 min-8 h	At concentrations >40 ppm lacrimation, reddening of conjunctivae, increased respiration noted. Mortality occurred at 50 ppm after 1 h with gasping and lung edema. Histologic signs included bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, edema.	Hine et al. 1970

Species	Route	Concentration	Duration	Effect	Reference
Guinea pig	Inhalation	2, 10 ppm	3 d continuously	At 10 ppm in 45-d old animals, toxicity included difficulty moving, reduced food and water consumption, hyperventilation. All exposed animals had reduced body weight after 45 d. 60% of 55-d old animals died at 10 ppm, most of them after 24 h exposure.	Azoulay-Dupuis et al. 1983
ACUTE TOXICITY (NONLETHAL)					
Rat	Inhalation	10, 25, 50, 100 ppm	5, 15, 30 min; 5, 15 min only	Pulmonary injury determined by lung weight found no change for exposure to 10 ppm for 30 min or 25-50 ppm for 15 min. Increased lung weight seen at 50 ppm for 30 min and 100 ppm for 5 and 15 min. Histologic changes for 25 ppm for 30 min, and 50 and 100 ppm for all durations included accumulation of fibrin, increased polymorphonuclear leukocytes and macrophages, extravasated erythrocytes, and type 11 pneumocyte hyperplasia.	Stavert and Lehnert 1990
Rat	Inhalation	25, 50, 75, 100, 150, 200, 250 ppm	5-30 min	Increased lung weights at ≥150 ppm for 5 min, 100 ppm for 15 min, 75 ppm for 30 min. Edema not proportional to duration. Histological changes, fibrin and type II cell hyperplasia seen at 50 ppm for 5 min. Severity increased proportionally.	Lehnert et al. 1994

	Rat	Inhalation	72, 90, 190 ppm	5, 15, or 60 min	Severe respiratory distress and eye irritation, increased lung-to-body-weight ratio increase, pulmonary edema, chronic murine pneumonia, darkened areas of lungs. Rats exposed to 104 ppm for 5 min, 65 ppm for 15 min, 28 ppm for 60 min, showed less respiratory distress, but increased weight ratios at 104 and 65 ppm, with no gross lesions, although pulmonary edema was evident. No clinical signs of toxicity at exposures of 74 and 33 ppm for 5 and 15 min, respectively.	Carson et al. 1962
	Rat	Inhalation	17 ppm	48 h	Histologic changes at 2 h included precapillary and postcapillary engorgement of alveoli, loss of cilia and alveolar type I cell swelling at 4 h, uniform terminal bronchiolar epithelium at 16 h, maximal macrophage numbers at 24 h, and cell hypertrophy and mitotic figure increases at 48 h.	Stephens et al. 1972
	Rat	Inhalation	20 ppm	20 h	Lung morphology changes included cytoplasmic blebbing in type I class, swelling and hyperplasia of type II cells, and interstitial edema at 5-15 d after exposure. Lungs normal at 35 d.	Hayashi et al. 1987
	Rat	Inhalation	10, 20, 30, 40 ppm	4 h	Alterations in lavage fluid seen at ≥ 20 ppm.	Guth and Mavis 1985
	Rat	Inhalation	100, 300, 1,000 ppm	1-20 min	Reductions in V_E increased with concentration. 7-15% for 15-20 min exposure to 100 ppm, and 20-28% reduction for 1-2 min exposure to 1,000 ppm.	Lehnert et al. 1994

Species	Route	Concentration	Duration	Effect	Reference
Mouse	Inhalation	5, 10, 20 ppm	24 h	At 10 and 20 ppm, increased lung wet weight and lung water content, at 5 ppm accelerated gaseous exchange and metabolic rate of oxygen and carbon dioxide but at higher concentration gaseous exchange was inhibited.	Suzuki et al. 1982
Mouse	Inhalation	20 ppm	4 d	Decreased food consumption and body weight, no deaths.	Bouley et al. 1986
Mouse	Inhalation	20 ppm	48 h	Decreased splenic and thymic weights, cellularity, plaque-forming cell response, and hemagglutins, and decreased body weight..	Azoulay-Dupuis et al. 1985
Mouse	Inhalation	20, 40 ppm	12 h	Suppressed primary antibody response	Hidekazu and Fujio 1981
Mouse	Inhalation	20 ppm	24 h	Minimal signs of irritation and behavior changes, questionable evidence of lung congestion and interstitial inflammation.	Hine et al. 1970
Mouse	Inhalation	50-140 ppm	1 h	Immediately after exposure to 140 ppm, visible cell death in terminal bronchioles, increase in protease inhibitor activity, pulmonary protein, and lung wet weights. Histologic damage increased at 48 h with progressive edema, congestion of lungs, hypertrophy and hyperplasia of epithelial cells, obliteration of alveolar structure, increased intraalveolar macrophages and neutrophils.	Siegel et al. 1989

Mouse	Inhalation	7, 9.2, 14.8 ppm; 2.3, 6.6 ppm	4 h post-infection; 17 h prior to infection	Decreased pulmonary bactericidal activity. Lungs of mice exposed to ≥ 9.2 ppm for 4 h had vascular hyperemia; those exposed to ≥ 2.3 ppm for 17 h had minor hyperemia and interstitial edema.	Goldstein et al. 1973
Monkeys	Inhalation	10, 15, 35, 50 ppm	2 h	Squirrel monkeys exposed to nitrogen dioxide alone had increased respiratory rate and decreased tidal volume at 35 and 50 ppm, but only slight effects at 10 and 15 ppm. Histologic changes more evident at the 2 higher concentrations. Challenge with *Kelbsiella pneumoniae* 24 h after exposure resulted in 3 of 3 monkeys dying with 72 h at 50 ppm exposure. No deaths with nitrogen dioxide exposure only.	Henry et al. 1969
Dog	Inhalation	39, 52, 53, 85, 125, 164 ppm	5-60 min	At 164 ppm for 5 min, 85 ppm for 15 min, and 53 ppm fo 60 min, signs of toxicity included respiratory distress during exposure, mild cough, eye irritation. At 125 pm for 5 min, 52 ppm for 15 min, or 39 ppm for 60 min, only mild sensory effects. No gross or microscopic lesions were seen in any dog.	Carson et al. 1962
Dog	Inhalation	1,000 ppm; 5,000 pm	136 min; 5-45 min	No effects in one dog exposed to 1,000 ppm; at 5,000 ppm for 15 and 22 min, evident respiratory distress with anxiety lasted 2 h.	Greenbaum et al. 1967
Dog	Inhalation	3-16 ppm	1 h	≥7 ppm, intraalveolar edema in most dogs, with ultrastructural alterations. At 3 ppm, formation in alveolar epithelium without biochemical or physiologic changes.	Dowell et al. 1971

Species	Route	Concentration	Duration	Effect	Reference
REPEATED EXPOSURES					
Rat	Inhalation	3.6-14.4 ppm	6-24 h/d, 3 d	Increases in protein content and cell types in lavage fluid.	Gelzleichter et al. 1992
Mouse	Inhalation	5 ppm	6 h/d, 4 d	Enhanced susceptibility to infection by murine cytomegalovirus followed by exposure to 5 ppm for 6 h/d for 4 d. No evidence of lung injury.	Rose et al. 1989
Mouse	Inhalation	4, 10, or 25 ppm	6 h/d, 5 d/wk, up to 21 d	At 4 ppm: no lesions in nasal cavity or lungs. At 10 ppm: no lesions in nasal cavity; increased cellularity of walls of bronchioles, alveolar duct, and adjacent alveoli by 21 d; hypertrophy or hyperplasia of small bronchi and bronchiolar epithelium by 7 d. At 25 ppm: no lesions in nasal cavity; hypertrophy or hyperplasia of small bronchi or bronchiolar epithelium by 7 d; increase in cellularity of walls of respiratory bronchioles, alveolar ducts, and adjacent alveoli by 7 d; some mononuclear infiltration of peribronchial areas.	Hooftman et al. 1988

Abbreviations: BAL, bronchoalveolar lavage; LC_{50}, median lethal concentration; LDH, lactic dehydrogenase; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; NR, not reported; V_E, minute volume of ventilation.

Repeated Exposure

Numerous repeated-exposure studies have been done with experimental animals (EPA 1993), although most have examined the effects of chronic exposures and thus are not relevant to setting SEALs. Several subchronic studies are summarized here. Gelzleichter et al. (1992) exposed rats at 3.6–14.4 ppm for 6–24 h/d for 3 d. The rats showed increases in protein content and cell types in lavage fluid. As mentioned above, mice exposed at 5 ppm for 6 h/d for 4 d exhibited enhanced susceptibility to infection by murine cytomegalovirus (Rose et al. 1989). Mice exposed at 10 or 25 ppm for 6 h/d, 5 d/wk for 21 d exhibited changes in their lungs (Hooftman et al. 1988). Mice exposed at 10 ppm had increased cellularity of the walls of the bronchioles, alveolar duct, and adjacent alveoli by 21 d and hypertrophy or hyperplasia of small bronchi and bronchiolar epithelium by 7 d; mice exposed at 25 ppm had hypertrophy or hyperplasia of small bronchi or bronchiolar epithelium by 7 d, an increase in cellularity of walls of respiratory bronchioles, alveolar ducts and adjacent alveoli by 7 d, and some mononuclear infiltration of peribronchial areas. Neither group nor another group exposed at 4 ppm had nasal lesions (Hooftman et al. 1988).

NAVY'S RECOMMENDED SEALS

The Navy proposes to set a SEAL 1 at 0.5 ppm and a SEAL 2 at 1 ppm. These levels were proposed to avoid even mild irritation to the eyes, nose, and upper respiratory tract.

RECOMMENDATIONS FROM OTHER ORGANIZATIONS

Recommended exposure guidance levels for nitrogen dioxide from other organizations are summarized in Table 8–4.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

In animals that survive exposure to nitrogen dioxide, the ciliated epithelium is killed and later replaced during healing, as it is after influenza. Lung phospholipids show free radicals after nitrogen dioxide exposure, but recover. Type I alveolar cells are damaged and become replaced by type II alveolar cells during recovery. Protein and fluid leak into the alveolar spaces and are reabsorbed. Inflammatory processes attract white cells into the lung tissue, and later

this resolves. There is less resistance of the lungs to infection by bacteria and viruses, requiring medical treatment. These processes are similar to the ones described for injurious but recoverable processes.

TABLE 8–4 Recommendations from Other Organizations for Nitrogen Dioxide

Organization	Type of Exposure Level	Recommended Exposure Level, ppm	Reference
ACGIH	TLV-TWA	3 ppm	ACGIH 1991, 1998
	TLV-STEL	5 ppm	
DFG	MAK (8h/d during 40-h workweek)	5 ppm	DFG 1997
	Peak Limit (5 min maximum duration, 8 times per shift)	10 ppm	
EPA	Primary and secondary ambient air quality standards	0.053 ppm, annual arithmetic mean concentration	EPA 1993
NIOSH	STEL	1 ppm	NIOSH 1994; Ludwig et al. 1994
	IDHL	20 ppm	
OSHA	Ceiling limit	5 ppm	OSHA 1996[a]

[a]Table 2–1. Limits for Air Contaminants. 29 CFR Part 1910.1000.

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; DFG, Deutsche Forschungsgemeinschaft; EPA, Environmental Protection Agency; IDLH, immediately dangerous to life and health; MAK, maximum allowable concentration in the workplace; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; STEL, short-term exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

A greater degree of inflammation can lead to permanent lung damage or death. The respiratory bronchioles become obliterated (bronchiolitis obliterans), the alveoli are filled with proteinaceous edema fluid (heavy, wet lungs), and the inflammatory process can turn into interstitial fibrosis.

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 0.5 ppm for nitrogen dioxide is too conservative. The subcommittee recom

mends a SEAL 1 for nitrogen dioxide of 5 ppm. The subcommittee's recommended SEAL 1 was derived by reducing the SEAL 2 of 10 ppm (see below for derivation of SEAL 2) to 5 ppm to avoid health effects from continuous exposure of up to 10 d. That reduction was based on the knowledge that the toxicity of nitrogen dioxide is more dependent on concentration than on exposure duration.

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 1 ppm for nitrogen dioxide is too conservative. The subcommittee recommends a SEAL 2 of 10 ppm for nitrogen dioxide. The subcommittee's recommendation is based on a study in which volunteers exposed at 30 ppm for 2 h experienced a burning sensation in the nose and chest, cough, dyspnea, and sputum production (NRC 1977). Also, animals (rats, mice, guinea pigs, rabbits, and dogs) exposed at 20 ppm for 24 h showed respiratory irritation and changes in behavior, possible lung congestion, and interstitial inflammation (Hine et al. 1970). The subcommittee concludes that the crew of a disabled submarine should be able to tolerate the irritant effects from exposure to nitrogen dioxide at concentrations below 10 ppm for up to 24 h.

DATA GAPS AND RESEARCH NEEDS

Studies in humans and experimental animals should be conducted to better define the dose-response curve for exposures to nitrogen dioxide lasting 10 h to 10 d. Nitrogen dioxide is a particularly reactive gas and therefore, its interaction with other combustion gases likely to be found in a disabled submarine should be studied.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Nitrogen Dioxide. Pp. 1108–1110 in Documentation of the Threshold Limit Values and Biological Exposure Indices, Vol. II, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1998. Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Adams, W.C., K.A.Brookes, and E.S.Schelegle. 1987. Effects of NO_2 alone and in combination with O_3 on young men and women. J. Appl. Physiol. 62(4):1698–1704.

Azoulay-Dupuis, E., M.Torrres, P.Soler, and J.Moreau. 1983. Pulmonary NO_2 toxicity in neonate and adult guinea pigs and rats. Environ. Res. 30(2):322–339.

Azoulay-Dupuis, E., M.Levacher, M.Muffat-Joly, and J.J.Pocidalo. 1985. Humoral immunodepression following acute NO_2 exposure in normal and adrenalectomized mice. J. Toxicol. Environ. Health 15(1):149–162.

Bauer, M.A., M.J.Utell, P.E.Morrow, D.M.Speers, and F.R.Gibb. 1985. Route of inhalation influences airway responses to 0.30 ppm nitrogen dioxide in asthmatic subjects. Am. Rev. Respir. Dis. 131:A171.

Bouley, G., E.Azoulay-Dupuis, and C.Gaudebout. 1986. Impaired acquired resistance of mice to *Klebsiella pneumoniae* induced by acute NO_2 exposure. Environ. Res. 41(2):497–504.

Budavari, S., M.J.O'Neil, A.Smith, P.E.Heckelman, and J.F.Kinneary, eds. 1996. Pp. 1135 in The Merck Index, 12th Ed. Rahway, NJ: Merck.

Carson, T.R., M.S.Rosenholtz, F.T.Wilinski, and M.H.Weeks. 1962. The responses of animals inhaling nitrogen dioxide for single, short-term exposures. Am. Ind. Hyg. Assoc. J. 23:457–462.

Devalia, J.L., C.Rusznak, M.J.Herdman, C.J.Trigg, H.Tarraf, and R.J.Davies. 1994. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 344(8938):1668–1671.

Devlin, R., D.Horstman, S.Becker, T.Gerrity, M.Madden, and H.Koren. 1992. Inflammatory response in humans exposed to 2.0 ppm NO_2. Am. Rev. Respir. Dis. 145:A 456.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, 1st Ed. Report No. 33. Weinheim: Wiley-VCH.

Douglas, W.W., N.G.G.Hepper, and T.V.Colby. 1989. Silo-filler's disease. Mayo Clin. Proc. 64 (3):291–304.

Dowell, A.R., K.H.Kilburn, and P.C.Pratt. 1971. Short-term exposure to nitrogen dioxide: Effects on pulmonary ultrastructure, compliance, and the surfactant system. Arch. Intern. Med. 128 (1):74–80.

DuBois, A.B., J.S.Douglas, J.T.Stitt, and V.Mohsenin. 1998. Production and absorption of nitric oxide gas in the nose. J. Appl. Physiol. 84(4):1219–1224.

Elsayed, N.M. 1994. Toxicity of nitrogen dioxide: An introduction. Toxicology 89(3):161–174.

EPA (U.S. Environmental Protection Agency). 1990. Research and Development: Health and Environmental Effects Document for Nitrogen Dioxide. ECAO-CING060. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Cincinnati, OH. 133 pp. March.

EPA (U.S. Environmental Protection Agency). 1993. Air Quality Criteria for Oxides of Nitrogen, Vol. I-II. EPA600/8–91/049aF. EPA600/8–91/049bF. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Research Triangle Park, NC. August.

Folinsbee, L.J., S.M.Horvath, J.F.Bedi, and J.C.Delehunt. 1978. Effect of 0.62 ppm

NO_2 on cardiopulmonary function in young male nonsmokers. Environ. Res. 15(2):199–205.

Frampton, M.W., P.E.Morrow, C.Cox, F.R.Gibb, D.M.Speers, and M.J.Utell. 1991. Effects of nitrogen dioxide exposure on pulmonary function and airway reactivity in normal humans. Am. Rev. Respir. Dis. 143(3):522–527.

Frampton, M.V., K.Z.Voter, P.E.Morrow, N.J.Roberts Jr., J.B.Gavras, and M.J.Utell. 1992. Effects of NO_2 on human host defense. Am. Rev. Respir. Dis. 145(4):A455.

Gamble, J., W.Jones, and S.Minshall. 1987. Epidemiological-environmental study of diesel bus garage workers: Acute effects of NO_2 and respirable participate on the respiratory system. Environ. Res. 42(1):201–214.

Gelzleichter, T.R., H.Witschi, and J.A.Last. 1992. Concentration-response relationships of rat lungs to exposure of oxidant air pollutants: A critical test of Haber's law for ozone and nitrogen dioxide. Toxicol. Appl. Pharmacol. 112(1):73–80.

Goings, S.A.J., T.J.Kulle, R.Bascom, L.R.Sauder, D.J.Green, J.K.Hebel, and M.L. Clements. 1989. Effect of nitrogen dioxide exposure on susceptibility to influenza A virus infection in healthy adults. Am. Rev. Respir. Dis. 139(5):1075–1081.

Gold, A., W.A.Burgess, and E.V.Clougherty. 1978. Exposure of firefighters to toxic air contaminants. Am. Ind. Hyg. Assoc. J. 39(7):534–539.

Goldstein, E., M.C.Eagle, and P.D.Hoeprich. 1973. Effect of nitrogen dioxide on pulmonary bacterial defense mechanisms. Arch. Environ. Health 26:202–204.

Goldstein, E., N.F.Peek, N.J.Parks, H.H.Hines, E.P.Steffey, and B.Tarkington. 1977. Fate and distribution of inhaled nitrogen dioxide in Rhesus monkeys. Am. Rev. Resp. Dis. 115 (3):403–412.

Goldstein, I.F., K.Lieber, L.K.Andrews, F.Kazembe, G.Foutrakis, P.Huang, and C. Hayes. 1988. Acute respiratory effects of short-term exposures to nitrogen dioxide. Arch. Environ. Health 43(2):138–142.

Gray, E.LeB., F.M.Patton, S.B.Goldberg, and E.Kaplan. 1954. Toxicity of the oxides of nitrogen. II. Acute inhalation toxicity of nitrogen dioxide, red fuming nitric acid, and white fuming nitric acid. Arch. Ind. Hyg. Occup. Med. 10:418–422.

Grayson, R.R. 1956. Silage gas poisoning: Nitrogen dioxide pneumonia, a new disease in agricultural workers. Ann. Int. Med. 45(3):393–408.

Greenbaum, R., J.Bay, M.D.Hargreaves, M.L.Kain, G.R.Kelman, J.F.Nunn, C.PrysRoberts, and K.Siebold. 1967. Effects of higher oxides of nitrogen on the anaesthetized dog. Brit. J. Anaesth. 39(5):393–404.

Guth, D.J., and R.D.Mavis. 1985. Biochemical assessment of acute nitrogen dioxide toxicity in rat lung. Toxicol. Appl. Pharmacol. 81(1):128–138.

Hackney, J.D., F.C.Thiede, W.S.Linn, E.E.Pedersen, C.E.Spier, D.C.Law, and D.A. Fischer. 1978. Experimental studies on human health effects of air pollutant. IV. Short-term physiological and clinical effects of nitrogen dioxide exposure. Arch. Environ. Health 33(4):176–181.

Harrington, W., and A.J.Krupnick 1985. Short-term nitrogen dioxide exposure and acute respiratory disease in children. J. Air Pollut. Control. Assoc. 35(10):1061–1067.

Hasselblad, V., D.M.Eddy, and D.J.Kotchmar. 1992. Synthesis of environmental evidence: Nitrogen dioxide epidemiology studies. J. Air Waste Manage. Assoc. 42(5):662–671.

Hayashi, Y., T.Kohno, and H.Ohwada. 1987. Morphological effects of nitrogen dioxide on the rat lung. Environ. Health Perspect. 73:135–145.

Hazucha, M.J., L.J.Folinsbee, E.Seal, and P.A.Bromberg. 1994. Lung function response of healthy women after sequential exposures to NO_2 and O_3. Am. J. Respir. Crit. Care Med. 150 (3):642–647.

Helleday, R., D.Huberman, A.Blomberg, N.Stjernberg, and T.Sandström. 1995. Nitrogen dioxide exposure impairs the frequency of the mucociliary activity in healthy subjects. Eur. Respir. J. 8(10):1664–1668.

Henry, M.C., R.Ehrlich, and W.H.Blair. 1969. Effect of nitrogen dioxide on resistance of squirrel monkeys to *Klebsiella pneumoniae* infection. Arch. Environ. Health 18(4):580–587.

Hidekazu, F., and S.Fujio. 1981. Effects of acute exposure to nitrogen dioxide on primary antibody response. Arch. Environ. Health 36(3):114–119.

Hine, C.H., F.H.Meyers, and R.W.Wright. 1970. Pulmonary changes in animals exposed to nitrogen dioxide, effects of acute exposures. Toxicol. Appl. Pharmacol. 16(1):201–213.

Hooftman, R.N., C.F.Kuper, and L.M.Appelman. 1988. Comparative sensitivity of histo-pathology and specific lung parameters in the detection of lung injury. J. Appl. Toxicol. 8(1):59–65.

Kerr, H.D., T.J.Kulle, M.L.McIlhany, and P.Swidersky. 1978. Effects of Nitrogen Dioxide on Pulmonary Function in Human Subjects, An Environmental Chamber study. EPA/6001/1–78/025. Office of Research and Development, Health Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC. 20pp.

Kleinman, M.T., R.M.Bailey, W.S.Linn, K.R.Anderson, J.D.Whynot, D.A.Shamoo, and J.D.Hackney. 1983. Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. J. Toxicol. Environ. Health 12(4–6):815–826.

Koenig, J.Q., D.S.Covert, M.S.Morgan, M.Horike, N.Horike, S.G.Marshall, and W.E. Pierson. 1985. Acute effects of 0.12 ppm ozone or 0.12 ppm nitrogen dioxide on pulmonary function in healthy and asthmatic adolescents. Am. Rev. Respir. Dis. 132(3):648–651.

Koenig, J.Q., D.S.Covert, S.G.Marshall, G.van Belle, and W.E.Pierson. 1987. The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. Am. Rev. Respir. Dis. 136(5):1152–1157.

Lehnert, B.E., D.C.Archuleta, T.Ellis, W.S.Session, N.M.Lehnert, L.R.Gurley, and D.M.Stavert. 1994. Lung injury following exposure of rats to relatively high mass concentrations of nitrogen dioxide. Toxicology 89(3):239–277.

Linn, W.S., and J.D.Hackney. 1983. Short-Term Human Respiratory Effects of Nitrogen Dioxide: Determination of Quantitative Dose-Response Profiles. Phase 1. Exposure of Healthy Volunteers to 4 ppm NO_2. CRC-CAPM-48–83.(1–82). Final Report. Rancho Los Amigos Hospital, Inc., Downey, CA. NTIS PB84–132299. 30 pp.

Linn, W.S., and J.D.Hackney. 1984. Short-Term Human Respiratory Effects of Nitrogen Dioxide: Determination of Quantitative Dose-Response Profiles. Phase 2.

Exposure of Asthmatic Volunteers to 4 ppm NO_2. CRC-CAPM-48–83.(1–82). Final Report. Rancho Los Amigos Hospital, Inc., Downey, CA. NTIS PB85–104388. 31 pp.

Love, G.J., S.P.Lan, C.M.Shy, and W.B.Riggan. 1982. Acute respiratory illness in families exposed to nitrogen dioxide ambient air pollution in Chattanooga, Tennessee. Arch. Environ. Health 37(2):75–80.

Lowry, T., and L.M.Schuman. 1956. "Silo-filler's disease"—a syndrom caused by nitrogen dioxide. J. Am. Med. Assoc. 162(3):153–160.

Ludwig, H.R., S.G.Cairell, and J.J.Whalen. 1994. Pp. 352 in Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHS). Cincinnati, OH: National Institute for Occupational Safety and Health. PB94–195047, National Technical Information Service, Springfield, VA.

Meulenbelt, J., J.A.Dormans, M.Marra, P.J.A.Rombout, and B.Sangster. 1992a. Rat model to investigate the treatment of acute nitrogen dioxide intoxication. Human Exp. Toxicol. 11 (3):179–187.

Meulenbelt, J., L.van Bree, J.A.Dormans, A.B.Boink, and B.Sangster. 1992b. Biochemical and histological alterations in rats after acute nitrogen dioxide intoxication. Human Exp. Toxicol. 11(3):189–200.

Meulenbelt, J., L.van Bree, J.A.Dormans, A.B.Boink, and B.Sangster. 1994. Development of a rabbit model to investigate the effects of acute nitrogen dioxide intoxication. Human Exp. Toxicol. 13(11):749–759.

Milne, J.E.H. 1969. Nitrogen dioxide inhalation and bronchiolitis obliterans. A review of the literature and report of a case. J. Occup. Med. 11(10):538–547.

Mohsenin, V. 1987. Airway responses to nitrogen dioxide in asthmatic subjects. J. Toxicol. Environ. Health 22(4):371–380.

Mohsenin, V. 1994. Human exposure to oxides of nitrogen at ambient and supra-ambient concentrations. Toxicology 89(3):301–312.

Mohsenin, V., and J.B.L.Gee. 1987. Acute effect of nitrogen dioxide exposure on the functional activity of alpha-1-protease inhibitor in bronchoalveolar lavage fluid of normal subjects . Am. Rev. Respir. Dis. 136(3):646–650.

Morley, R., and S.J.Silk. 1970. The industrial hazard from nitrous fumes. Ann. Occup. Hyg. 13 (2):101–107.

Morrow, P.E., M.J.Utell, M.A.Bauer, A.M.Frampton, C.Cox, D.M.Speers, and F.R. Gibb. 1992. Pulmonary performance of elderly normal subjects and subjects with chronic obstructive pulmonary disease exposed to 0.3 ppm nitrogen dioxide. Am. Rev. Respir. Dis. 145(2Part 1):291–300.

NIOSH (National Institute for Occupational Safety and Health). 1994. Pp. 228 in NIOSH Pocket Guide to Chemical Hazards. Cincinnati, OH: U.S. Dept. of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

Norwood, W.D., D.E.Wisehart, C.A.Earl, F.E.Adley, and D.E.Anderson. 1966. Nitrogen dioxide poisoning due to metal-cutting with oxyacetylene torch. J. Occup. Med. 8(6):301–306.

NRC (National Research Council). 1977. Medical and Biologic Effects of Environmental Pollutants. Nitrogen Oxides. Washington, DC: National Academy of Sciences. 333 pp.

NRC (National Research Council). 1985. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

Oda, H., H.Tsubone, A.Suzuki, T.Ichinose, and K.Kubota. 1981. Alterations of nitrite and nitrate concentrations in the blood of mice exposed to nitrogen dioxide. Environ. Res. 25(2):294–301.

Orehek, J., J.P.Massari, P.Gayrard, C.Grimaud, and J.Charpin. 1976. Effect of shorterm, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J. Oin. Invest. 57 (2):301–307.

Pilotto, L.S., R.M.Douglas, R.G.Attewell, and S.R.Wilson. 1997. Respiratory effects associated with indoor nitrogen dioxide exposure in children. Int. J. Epidemiol. 26(4):788–796.

Posin, C., R.D.Buckley, K.Clark, J.D.Hackney, M.P.Jones, and J.V.Patterson. 1978. Nitrogen dioxide inhalation and human blood biochemistry. Arch. Environ. Health 33(6):318–324.

Postlethwait, E.M., and A.Bidani. 1990. Reactive uptake governs the pulmonary airspace removal of inhaled nitrogen dioxide. J. Appl. Physiol. 68(2):594–603.

Postlethwait, E.M., and A.Bidani. 1994. Mechanisms of pulmonary NO_2 absorption. Toxicology 89 (3):217–237.

Postlethwait, E .M., and M.G.Mustafa. 1981. Fate of inhaled nitrogen dioxide in isolated perfused rat lung. J. Toxicol. Environ. Health 7(6):861–872.

Rasmussen, T.R., S.K.Kjaergaard, U.Tarp, and O.F.Pedersen. 1992. Delayed effects of NO_2 exposure on alveolar permeability and glutathione peroxidase in healthy humans. Am. Rev. Respir. Dis. 146(3):654–659.

Roger, L.J., D.H.Horstman, W.McDonnell, H.Kehrl, P.J.Ives, E.Seal, R.Chapman, and E.Massaro. 1990. Pulmonary function, airway responsiveness, and respiratory symptoms in asthmatics following exercise in NO_2. Toxicol. Ind. Health 6(1):155– 171.

Rose, R.M., P.Pinkston, and W.A.Skornik. 1989. Altered susceptibility to viral respiratory infection during short-term exposure to nitrogen dioxide. Res. Rep. Health Eff. Inst. 24:1–24.

Rubinstein, I., B.G.Bigby, T.F.Reiss, and H.A.Boushey Jr. 1990. Short-term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway responsiveness to sulfur dioxide in asthmatic subjects. Am. Rev. Respir. Dis. 141(2):381–385.

Russell, M.L., J.L.Need, R.R.Mercer, F.J.Miller, and J.D.Crapo. 1991. Distribution of inhaled $[^{15}O]^{-}$ NO_2 in the upper and lower respiratory tracts of rats. Am. Rev. Respir. Dis. 143(4 Pt 2):A704.

Sackner, M.A., S.Birch, A.Friden, and C.Marchetti. 1981. Effects of breathing low levels of nitrogen dioxide for four hours on pulmonary function of asthmatic adults. Am. Rev. Respir. Dis. 123(4 Pt 2):151.

Saul, R.L., and M.C.Archer. 1983. Nitrate formation in rats exposed to nitrogen dioxide. Toxicol. Appl. Pharmacol. 67(2):284–291.

Shy, C.M., J.P.Creason, M.E.Pearlman, K.E.McClain, F.B.Benson, and M.M.Young. 1970a. The Chattanooga school children study: Effects of community exposure to nitrogen dioxide. I. Methods, description of pollutant exposure, and results of ventilatory function testing. J. Air Pollut. Control Assoc. 20(8):539–545.

Shy, C.M., J.P.Creason, M.E.Pearlman, K.E.McClain, F.B.Benson, and M.M.Young. 1970b. The Chattanooga school children study: Effects of community exposure to nitrogen dioxide. II. Incidence of respiratory illness. J. Air Pollut. Control Assoc. 20(9):582–588.

Siegel, P.D., B.E.Bozelka, C.Reynolds, and W.J.George. 1989. Phase-dependent response of the lung to NO_2 irritant insult. J. Environ. Pathol. Toxicol. Oncol. 9(4):303–315.

Speizer, F.E., and B.G.Ferris Jr. 1973. Exposure to automobile exhaust. I. Prevalence of respiratory symptoms and disease. Arch. Environ. Health 26(6):313–318.

Stavert, D.M. and B.E.Lehnert. 1990. Nitric oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for brief periods. Inhalation Toxicol. 2:53–67.

Stephens, R.J., G.Freeman, and M.J.Evans. 1972. Early response of lungs to low levels of nitrogen dioxide. Light and electron microscopy. Arch. Environ. Health 24(3):160–179.

Suzuki, A.K., H.Tsubone, and K.Kubota. 1982. Changes in gaseous exchange in the lung of mice acutely exposed to nitrogen dioxide. Toxicol. Lett. 10(4):327–355.

Tse, R.L., and A.A.Bockman. 1970. Nitrogen dioxide toxicity: report of four cases in firemen. JAMA 212(8):1341–1344.

Tunnicliffe, W.S., P.S.Burge, and J.G.Ayres. 1994. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 344(8939–8940):1733–1736.

Utell, M.J., and P.E.Morrow. 1989. Responses of Susceptible Subpopulations to Nitrogen Dioxide. Research Report No 23. Cambridge, MA: Health Effects Institute.

Vagaggini, B., P.L.Paggiaro, D.Giannini, A.Di Franco, S.Cianchette, S.Carnevali, M. Taccola, E.Bacci, L.Bancalari, F.L.Dente, and C.Giuntini. 1996. Effect of short-term NO_2 exposure on induced sputum in normal, asthmatic, and COPD subjects. Eur. Respir. J. 9(9):1852–1857.

Von Nieding, G., and H.M.Wagner. 1979. Effects of NO_2 on chronic bronchitics. Environ. Health Perspect. 29:137–142.

9

Sulfur Dioxide

This chapter reviews the physical and chemical properties and toxicokinetic, toxicologic, and epidemiologic data on sulfur dioxide. The Subcommittee on Submarine Escape Action Levels used this information to assess the health risk to Navy personnel aboard a disabled submarine and to evaluate the submarine escape action levels (SEALs) proposed to avert serious health effects and substantial degradation in crew performance from short-term exposures (up to 10 d). The subcommittee also identifies data gaps and recommends research relevant for determining the health risk attributable to exposure to sulfur dioxide.

BACKGROUND INFORMATION

Sulfur dioxide is a colorless, water-soluble irritant gas (Costa and Amdur 1996). It can be detected by taste at concentrations of 0.35–1.05 ppm (parts per million) and has an immediate pungent irritating odor at a concentration of 3.5 ppm (WHO 1984). It has been termed a “mild irritant” (Amdur 1969). Ambient sulfur dioxide can react with oxygen to form sulfur trioxide, which then reacts with water (on moist surfaces) to produce sulfuric acid. Sulfur dioxide also can react with water to form sulfurous acid, which dissociates to sulfite and bisulfite ions. The chemical and physical properties of sulfur dioxide are presented in Table 9–1.

TABLE 9–1 Physical and Chemical Properties for Sulfur Dioxide

Characteristic	Value
Molecular formula	SO_2
Synonyms	Sulfurous anhydride, sulfurous oxide, sulfur oxide, sulfurous acid anhydride
Molecular weight	64.07
CAS number	7446–09–5
Solubility	Soluble in water, alcohol, acetic acid, sulfuric acid, ether, and chloroform
Density	2.811 g/L
Vapor pressure	3×10^{-3} mm Hg at 25°C
Saturated vapor pressure	0.47 lb/ft^3 at 15°C
Melting point	–72°C
Boiling point	–10°C
Conversion factors in air, 1 atm	1 ppm=2.6 mg/m^3 1 mg/m^3=0.38ppm

Abbreviation: CAS, Chemical Abstracts Service.
Source: NRC (1984); Budavari (1989); ACGIH (1994); ATSDR (1998); HSDB (2000).

Sulfur dioxide is formed when materials containing sulfur are burned. It is a primary air pollutant emitted by smelters and electrical power plants that burn coal or oil. Sulfur dioxide is found at concentrations of 1–10 parts per billion (ppb) in clean ambient air, and at 20–200 ppb in polluted air (Seinfeld 1986). Sulfur dioxide also is used in treating wood pulp for paper manufacturing; in ore and metal refining; in extraction of lubricating oils; as a bleaching, disinfecting, and fumigating agent; as a food additive and preservative; and as a reducing agent. Sulfur dioxide is a precursor to acid sulfates, which generally are more toxic; therefore, recent research has focused on those compounds (Costa and Amdur 1996).

TOXICOKINETIC CONSIDERATIONS

Absorption

Sulfur dioxide is primarily an upper airway and eye irritant. In the airways, it produces bronchoconstriction and mucous secretion. Because of its high water

solubility, sulfur dioxide appears to react in airway and lung fluids to produce sulfite (SO_3^{2-}) or bisulfite (HSO_3^-) ions, but itself can be rapidly absorbed. The bisulfite ion is a direct irritant and it inhibits mucociliary transport (Costa and Amdur 1996). The irritation results in parasympathetic stimulation producing smooth muscle contraction and mucous secretion (HSDB 2000).

Studies in humans and animals suggest that 40–90% of inhaled sulfur dioxide is absorbed in the upper respiratory tract (WHO 1979). Two factors affect the efficiency of absorption in the respiratory tract: the mode of breathing (oral versus oronasal) and the ventilation rate. Penetration of sulfur dioxide to the lungs is greater during mouth breathing than during nose breathing, as sulfur dioxide is readily removed during passage through the upper respiratory tract. An increase in ventilation rate, for example during exercise, increases penetration of sulfur dioxide to the deeper lung (Costa and Amdur 1996).

In rabbits exposed to 100, 200, or 300 ppm, 90–95% of the sulfur dioxide was found to be absorbed by tissues in the upper respiratory tract (Dalhamn and Strandberg 1961), and the rate of absorption in the nasal cavity was greater than that in the mouth or pharynx. Strandberg (1964) determined that in rabbits, the amount of sulfur dioxide absorbed depends on concentration. Rabbits exposed to high concentrations (≥100 ppm) had ≥90% absorption; at low concentrations (≥0.1 ppm), absorption was about 40%. The reasons for these different rates of absorption with varying concentration are not clear. In dogs, more than 99% of inhaled sulfur dioxide is absorbed by the nose at exposure of 2.9–140 mg/m^3 (1–50 ppm). Similar absorption rates have been observed in studies of human volunteers who were exposed to concentrations ranging from 2.9 to 420 mg/m^3 (1–140 ppm) for a few minutes at the higher concentrations and for 30–40 min at the lower concentrations (WHO 1979).

Speizer and Frank (1966) observed that, in human subjects breathing through a mask and exposed to 16.1 ppm for 30 min, 12% of the sulfur dioxide taken up by the tissues in inspiration reentered the airstream in expiration and that another 3% was desorbed during the first 15 min after the end of the exposure. The authors concluded that 12–15% of sulfur dioxide absorbed on nasal mucosa is desorbed and exhaled. The remaining sulfur dioxide and metabolites are absorbed into the systemic circulation or are delivered to the lower respiratory system by repeated absorption and desorption from mucosa (Frank et al. 1969). Frank et al. (1967) reported sulfur dioxide in the lungs of dogs that apparently was carried by the blood after nasal deposition. Systemic absorption of sulfur dioxide metabolites from tissues of the upper respiratory tract has been demonstrated in animals. In dogs a small segment of trachea was isolated and perfused with radiolabeled sulfur dioxide ($^{35}SO_2$) while the lungs were ventilated with auto prevent entry of the $^{35}SO_2$ (Balchum et al. 1959). Detection of ^{35}S in lungs, liver, spleen, and kidneys indicated systemic absorption from the tracheal mucosa.

Distribution

Most inhaled sulfur dioxide is absorbed into the bloodstream, widely distributed throughout the body, and rapidly metabolized to sulfate by the sulfite oxidase enzyme system. Sulfate is then primarily excreted by way of the urinary tract (HSDB 2000). However, results from studies that used ^{35}S indicate that some residual sulfur dioxide can persist in the respiratory system for a week or more after exposure possibly as a result of the sulfur binding with protein (Yokoyama et al. 1971 as cited in Costa and Amdur 1996).

In rabbits and human subjects, sulfite (metabolite of sulfur dioxide) that reaches the plasma has been shown to form S-sulfonate products ($R\text{-}S\text{-}SO_3^-$) by reacting with the disulfide bonds of proteins (Gunnison and Palmes 1974). Gunnison and Palmes (1974) exposed human subjects continuously to 0.3, 1.0, 3.0, 4.2, or 6.0 ppm sulfur dioxide for up to 12 h, determined that plasma sulfonate concentrations had a positive correlation with air concentrations of sulfur dioxide. Although the biochemical significance of these S-sulfonate products is not currently understood, their formation represents a biochemical alteration (Costa and Amdur 1996).

Studies with dogs suggest that absorbed sulfur dioxide metabolites are readily distributed throughout the body (Frank et al. 1967; Yokoyama et al. 1971). Frank et al. (1969) exposed dogs to 22±2 ppm $^{35}SO_2$ for 30–60 min and deteched radioactivity in the blood 5 min after the onset of exposure. It was estimated that 5% to 18% of the radioactive compound administered to the dogs was contained in the blood by the end of exposure. Balchum et al. (1959, 1960 a,b) examined radioactivity in dogs administered $^{35}SO_2$. Dogs that inhaled $^{35}SO_2$ through the nose and mouth at concentrations of 1–141 ppm had significant radioactivity in the upper airways; lower rates were exhibited in the trachea, lungs, hilar lymph nodes, liver, and spleen.

Metabolism

Although the primary effects of sulfur dioxide are on the respiratory tract, inhaled sulfur dioxide can be transferred into the systemic circulation. After its rapid absorption, inhaled sulfur dioxide is rapidly converted to a mixture of sulfite, bisulfite, and sulfur trioxide (ATSDR 1998):

$$SO_2 + H_2O \Leftrightarrow H_2SO_3 \underset{-H^+}{\overset{+H^+}{\Leftrightarrow}} HSO_3^- \underset{-H^+}{\overset{+H^+}{\Leftrightarrow}} SO_3^{2-}$$

Sulfite and bisulfite ions can be oxidized to form plasma protein S-sulfonates. Bisulfite is further detoxified by sulfite oxidase, which is found primarily in liver mitochondria (Gunnison et al. 1987) and is excreted as sulfate ion in the urine. Sulfite oxidase also has been detected in other tissues, including kidney and heart (Cabre et al. 1990).

Sulfite oxidase concentrations vary in animals and humans, and the efficiency of sulfite oxidation depends primarily on sulfite oxidase activity (Gunnison and Palmes 1974). Cohen et al. (1973) observed sulfite oxidase activity to be lower in the livers of young versus mature rats, sulfite oxidase activity in 1-d-old rats was one-tenth that of adults. Decreased activity of sulfite oxidase in sulfite-oxidase-deficient rats resulted in higher in vivo concentrations of sulfite, whereas sulfite-oxidase-competent rats exposed to sulfur dioxide lacked sulfite in the plasma (Gunnison et al. 1987).

In humans, age-related differences have been observed in metabolism of sulfite to sulfate and in formation of sulfur trioxide (Constantin et al. 1996). Constantin et al. (1996) measured sulfur trioxide radicals and sulfite oxidase activity in polymorphonuclear leukocytes (PMNs) from four groups: young adults (average age 25), older adults (average age 65), 3 centenarians (older than 100), and Down syndrome patients. They found significantly increased amounts of sulfur trioxide radicals in PMNs from healthy adults who had low sulfite oxidase activity. In centenarians and Down syndrome patients, generation of the sulfur trioxide radical was the primary mechanism for detoxification of sulfite. There was no correlation between the sulfur trioxide radical and sulfite oxidase activity.

Langley-Evans et al. (1996) observed decreased glutathione concentrations in the lungs of rats exposed to sulfur dioxide, suggesting that glutathione could operate in the detoxification process. Kågedal et al. (1986) conducted in vitro experiments demonstrating that sulfites—metabolites of sulfur dioxide—react with reduced glutathione to form S-sulfoglutathione.

Elimination

Studies on humans and dogs show that sulfur dioxide is excreted primarily in the urine as sulfate (Savic et al. 1987; Yokoyama et al. 1971). Yokoyama et al. (1971) exposed dogs via inhalation to $^{35}SO_2$ and determined that ^{35}S was excreted primarily in the urine as sulfate. An average of 84.4% of the urinary radioactivity was exhibited as inorganic sulfate; 92.4% was total sulfate. In humans it is estimated that 12–15% of sulfur dioxide absorbed to mucous membranes is desorbed and exhaled (Speizer and Frank 1966). Plasma S-sulfonates are relatively long-lived in the body, with half-life clearance of 4.1 d in rabbits exposed to 10 ppm sulfur dioxide (Gunnison and Palmes 1974).

HUMAN TOXICITY DATA

Many studies have examined the human health effects from exposure to sulfur dioxide. The next section examines the effects of experimental, accidental, occupational, and community exposures; however, more complete reviews are available in the *Toxicological Profile for Sulfur Dioxide* (ATSDR 1998); *Air Quality Criteria for Particulate Matter and Sulfur Oxides* (EPA 1982); and *Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982)* (EPA 1994a,b).

Experimental Studies

Table 9–2 summarizes exposure studies that used controlled exposures to sulfur dioxide. Mild irritation, bronchoconstriction, and decreased lung function, as assessed by measurements of specific airway resistance or decreases in forced expiratory volume or expiratory flow, are produced after exposure of healthy individuals to low concentrations of sulfur dioxide. People with asthma are more susceptible. Exercise, cold air, and airborne participates appear to exacerbate the toxic effects (Gong et al. 1995; Roger et al. 1985; Schachter et al. 1984; Stacy et al. 1981). Concentration seems to be more important than duration as a determinant of health effects. Initial atmospheric exposure to sulfur dioxide can result in immediate discomfort, irritation, and coughing that abate after gradual acclimation to increasing concentrations (Andersen et al. 1974). Health effects reported by healthy volunteers are summarized in Table 9–3.

Accidental Exposures

Several case reports detail accidental exposures to sulfur dioxide (Table 9–2). Those events involved inhalation and ocular exposures to unquantified concentrations, so dose-response determinations were not possible. Accidents have resulted in death, primarily from respiratory arrest (Charan et al. 1979; Galea 1964; Harkonen et al. 1983; Rabinovitch et al. 1989). Signs of intoxication preceding or found antecedent to death included bronchoconstriction, lung pathology, decreases in lung function; and ocular, nasal, and throat irritation (Charan et al. 1979; Galea 1964; Harkonen et al. 1983; Rabinovitch et al. 1989; Wunderlich et al. 1982). Survivors suffered bronchitis, bronchiolitis, bronchopneumonia, alveolitis, and emphysema (Galea 1964; Wunderlich et al. 1982).

TABLE 9-2 Human Toxicity Data, Exposure to Sulfur Dioxide

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
EXPERIMENTAL STUDIES					
14 healthy males	Inhalation	1-8	10 min (through face mask)	At 5 ppm, subjects complained of dryness in throat and upper respiratory passages; 1-8 ppm, decreased respiratory volume and increased respiratory rate were noted	Amdur et al. 1953
31 non-smoking males, aged 18-40 (individuals exercised on a treadmill 45 min after entering exposure chamber)	Inhalation and intra-dermal tests for 16 allergens, including sulfur dioxide	16 Individuals, 0.75 ± 0.04 ppm; 15 were exposed to air	2 h	Airflow resistance increased 2-55% in 14 of 16 subjects following the first hour of exposure. Average increase in exposed subjects was 14.6%; average 10.3% decrease in control subjects; 8 exposed subjects with 1 or more positive allergen skin tests appeared to be significantly more reactive than subjects who tested negative in skin tests	Stacy et al. 1981
8 healthy, nonsmoking individuals, 21-29 years (subjects exercised for the last 15 minutes of exposure)	Inhalation	0, 0.4, 2, or 4	20 min	At 4 ppm, 5 of 8 subjects reported nasal irritation; throat irritation was more common ($p < 0.05$) during than before exposure to 2 ppm; it was reported more frequently during and at the end of exposure to 4 ppm than before exposure ($p < 0.02$) and more commonly ($p < 0.05$) at the end of exposure to 4 ppm than at the end of 0.4 ppm exposure	Sandstrom et al. 1988
14 healthy subjects, aged	Inhalation	4 (10 subjects) or 8 (4 subjects)	20 min	BAL parameters were measured. At 4 and 8 ppm, an increase in alveolar	Sandstrom et al. 1989a

22-33 (individuals exercised during exposure)				macrophage activity (as measured by lysozyme positive macrophages) observed 24 h after exposure; at 8 ppm, an increase in total number of macrophages and lymphocytes; at 72 h, BAL fluid of 8 ppm exposure group returned to baseline.	
22 healthy males, aged 22-27 (individuals exercised during exposure)	Inhalation	8	20 min	BAL observed 2 wk before exposure, and 4, 8, 24, and 72 h after exposure in 8 subjects; at 4 h, increased numbers of lysozyme-positive macrophages, lymphocytes, and mast cells observed; lymphocytes, lysozyme-positive macrophages, total alveolar macrophage counts, and total cell numbers reached a peak at 24 h post-exposure and returned to pre-exposure levels by 72 h	Sandstrom et al. 1989b
22 healthy males, aged 22-37	Inhalation	4, 5, 8, or 11	20 min	BAL observed 2 wk before exposure, and 4, 8, 24, and 72 h after exposure in 8 subjects; at 4, 5, 8, and 11 ppm, mast cells, lymphocytes, lysozyme-positive macrophages, and total number of macrophages increased in BAL fluid 24-h post-exposure, with the effects being concentration-dependent at 4, 5, and 8 ppm	Sandstrom et al. 1989c
20 healthy, nonsmoking adults (10 females, 10	Inhalation	1 or filtered air	4 h	4 exposed subjects reported upper respiratory irritation and 1 reported ocular irritation; 7 exposed subjects perceived either due to odor and/or taste.	Kulle et al. 1984

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
males), aged 20-35 (each subject served as his/her own control and exercised for 15 min both 1 and 3 h into the exposure period)					
11 healthy adult males	Inhalation (mouth breathing)	0, 1, 5, or 13	10-30 min	At 13 and 5 ppm, pulmonary flow resistance was increased an average of 72% and 39% above that of controls; at 5 ppm, cough, irritation, and increased salivation also observed; 1 ppm, no treatment-related effects; authors concluded that peak response occurred after 5-10 min of exposure	Frank et al. 1962
6 healthy nonsmoking adult males	Inhalation (mouth breathing)	SO_2 at 1-2, 4-6, or 14-17 ppm, alone or in conjunction with NaCl aerosol (18 mg/m^3)	30 min	At 4-6 and 14-17 ppm SO_2 with or without NaCl, a concentration-dependent increase in pulmonary flow resistance was observed; at 1-2 ppm, no significant effects observed	Frank et al. 1964
11 healthy adult males	Inhalation (compari-	15, 29	10 min	At 15 and 29 ppm, pulmonary flow resistance increased 20% and 65% for	Frank 1964

	son was made between oral and nasal SO_2 administration)				mouth breathers and 3% and 18% for nose breathers	
11 healthy subjects	Inhalation	0.55	10 min		No nasal or ocular irritation reported	Dautrebrande and Capps 1950
Healthy subjects (number not specified)	Inhalation, dermal (subjects exposed wearing close-fitting goggles)	0, 1, 5	Ocular exposure: 15 s; inhalation subjects inhaled 10 breaths of 1 L at given concentration		5 ppm threshold for ocular irritation; 1 ppm threshold for broncho-constriction.	Douglas and Coe 1987
15 healthy males, aged 20-28	Inhalation	0, 1, 5, 25	6 h		At 25 and 5 ppm, dose-dependent decrease in nasal mucous flow; an increase in nasal flow resistance and a decrease in FEV1; at 1 ppm no observed effect; after exposure all but 1 of the 25 ppm subjects complained of irritative effects but none considered irritation "excessive"; 5 subjects exposed to 5 ppm complained of effects	Andersen et al. 1974

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
10 healthy men, aged 55-73	Inhalation	0.1 ppm of SO_2 and 1 mg/m^3 NaCl aerosol, 1 ppm SO_2 and 1 mg/m^3 NaCl aerosol, or 1 mg/m^3 NaCl aerosol alone	20 min at rest and 10 min during moderate exercise	Significant decreases in FEV_1 2-3 min after exposure in all groups; decrease observed after 1 ppm SO_2 and NaCl was significantly greater than after exposure to NaCl alone	Rondinelli et al. 1987
10 asthma patients subjects (4 males, 6 females, median age 27) and 10 healthy subjects (5 males, 5 females, median age 26 yr)	Inhalation	0, 0.25, 0.50, 0.75, 1	40 min (subjects exercised for first 10 min); on separate days subjects were exposed to 0 or 1 ppm in the absence of exercise	No significant effects observed in healthy individuals on any day, or in asthma patients at rest; in exercising asthma patients, exposure to 1 ppm resulted in significant changes from baseline in airway resistance, FEV_1, MEF at 60% of VC below total lung capacity on the partial flow volume curve [MEF40% (P)], and reductions in flows at ($V_{MAX50\%}$); no significant changes in these parameters observed at lower concentrations, with the exception of small decreases in $V_{MAX50\%}$ at 0.25 and 0.5 ppm; for exercising asthma patients, a dose-dependent relationship was observed: Average changes in airway resistance, FEV1, MEF40%, (P), and $V_{MAX50\%}$ increasing with SO_2 concentrations, with a	Schachter et al. 1984

					consistent effect first observed at 0.75 ppm; results suggest that asthma patients engaged in moderate activity have transient bronchoconstriction after exercise in the presence of SO_2, with consistent changes observed when concentrations reach 0.75 ppm	
	4 nonsmoking asthma patients (2 males, 2 females)	Inhalation	0.5	1, 3, 5 min	3-min exposure resulted in 173% increase in airway resistance; wheezing, chest tightness, dyspnea	Balmes et al. 1987
	22 asthma patients (13 males, 9 females, aged 18-33)	Inhalation	All possible combinations of the following: 2 exposures (purified air and 0.6 ppm); 2 temperatures (21°C, 38°C); 20%, 80% RH	~5 min during exercise	Symptom questionnaires and body plethysmographic measurements were completed before and after each exposure; exposure to 0.6 ppm in conjunction with low temperature and low humidity (21°C and 20% RH) tripled group mean specific airway resistance; however, exposure to 0.6 ppm and high humidity and high temperature (38°C, 80% RH) increased specific airway resistance by less than 40%	Linn et al. 1985
	14 asthma patients (13 males, 9 females, aged 18-33)	Inhalation	0, 0.5, 1.0	10 min during light, medium, or heavy exercise	At 0.5 ppm during light exercise, mild to moderate respiratory effects were reported, at 1.0 and heavy exercise, effects were reported as moderate to severe; effects reported as shortness of breath, wheezing, and chest tightness; both FEV_1 and SRaw showed significant	Gong et al. 1995

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
				exposure-related effects, but the authors comment that the exact magnitude is difficult to ascertain	
28 male asthma patients aged 19-34	Inhalation	0, 0.25, 0.50, 1	75 min (included 3 10-min periods of moderate treadmill exercise)	At 0.25 ppm there was no significant effect on SRaw; at 0.5 and 1.0 ppm, SRaw was increased two- and threefold above pre-exposure, respectively; increases were greatest after the first 10-min exercise period and less after the latter 2 10-min exercise periods; based on analysis of symptom questionnaires, only shortness of breath and chest discomfort were significantly increased after 10 min exposure to 1 ppm	Roger et al. 1985
14 asthma patients (10 males, 4 females, aged 20-55)	Inhalation	0, 0.5	30 min	Subjects exposed at rest.; no increase in SRaw observed; no exposure-related subjective symptoms noted	Jorres and Magnussen 1990
9 asthma patients (7 males, 2 females, aged 14-18)	Inhalation	Filtered air, 1 ppm SO_2 and 1 mg/m^3 NaCl aerosol, or 1 mg/m^3 NaCl aerosol alone	60 min (divided into 2 30-min periods with 5-7 min interruption when functional	Significant decreases in maximal flow at V_{MAX50} and V_{MAX75} observed after combined exposures; no significant changes observed during exposure to filtered air or NaCl droplet aerosol alone	Koenig et al. 1980

				measurements were taken)		
7 healthy subjects	Inhalation	4-6	10 min	Increased Raw as measured by body plethysmography	Nadel et al. 1965
Healthy subjects	Inhalation	1, 5	1 ppm (not reported); 5 ppm (10 min)	At 1 ppm SRaw increased after deep inhalation; at 5 ppm increased resistance during quiet mouth breathing	Lawther et al. 1975
Asthma patients	Inhalation	0.10, 0.25	10 min (individuals exercised during exposure)	Significant changes in Raw observed after 0.25 ppm exposure; most sensitive subjects exhibited some broncho-constriction, as evidenced by a slight increase in SRaw following inhalation at 0.1 ppm	Sheppard et al. 1981
27 asthmatics	Inhalation	0, 0.25, 0.50, 1.00	10 min (individuals exercised during exposure)	Determined the SO_2 concentration required to produce an increase in airway resistance 100% greater than the response to clean air (designated as $PC(SO_2)$); substantial variability in $PC(SO_2)$, median $PC(SO_2)$ at 0.75 ppm, with 23 subjects had $PC(SO_2)$ from 0.28-1.90; 4 subjects had $PC(SO_2)$ above 2.0	Horstman et al. 1986
5 male paper mill workers	Inhalation, dermal	NR		2 workers accidentally exposed to SO_2 under pressure; workers died within 5 min; 3 other workers exposed to lower concentrations experienced acute symptoms including ocular, nasal, and throat irritation and soreness, chest tightness, and intense dyspnea; severe	Charan et al. 1979

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
				conjunctivitis and superficial corneal burns; the pharyngeal mucosa hyperemic but free of ulcerations.	
2 male pulp and paper mill workers	Inhalation	NR	15-20 min	1 worker survived, but exhibited delayed chronometric vital capacity, prolonged expiratory phase, and marked respiratory fatigue 4 mo after exposure; the other worker died 17 d after the accident, showing evidence of acute emphysematous changes, including peribronchiolar fibrosis and bronchiolotis obliterans	Galea 1964
3 healthy male cooper mineworkers	Inhalation, dermal	>40	3.5 h (for 2 survivors)	Copper iron sulfide dust explosion; 1 miner died within minutes. The other 2 experienced intense burning of eyes, nose, and throat; dyspnea; diffuse precordial and retro sternal chest pain; nausea, vomiting; urinary incontinence. 3 wk after the exposure, the workers had severe airway obstruction, hypoxemia, markedly decreased exercise tolerance, ventilation-perfusion mismatch, evidence of active inflammation (positive gallium scan)	Rabinovitch et al. 1989
9 healthy workers	Inhalation	NR (pyrite (FeS_2) explosion in a	20-45 min	1 worker died; lung function of survivors was followed for 4 yr; the largest decreases in FVC; FEV_1, and maximal	Harkonen et al. 1983

		mine)		midexpiratory flow were seen at 1 wk, spirometry indicated obstructive findings in 6 workers, restrictive findings in 1 worker; at 3 mo, no further lung function decrement occurred; however, 4 y after the accident, reversible bronchiolar obstruction still present in 3 workers	
Male aged 12	Inhalation, dermal	4.8 (concentration measured several days after exposure)	4 min	Accidental fall into a pit containing SO_2; subject presented with acute irritation of eyes and mucous membranes of the upper airways, rhinopharyngitis, laryngitis, bonchitis, conjunctivitis, and corneal lesions; effects persisted for 5 d and then were followed by a symptom-free 3-d period. The following symptoms persisted for 12 mo: obstructing bronchitis; bonchiolitis; alveolitis; emphysema of the lung; mediastinum, and skin; bronchiectasis then developed and persisted for 12 mo. Lung emphysema and continuous partial respiratory insufficiency, accompanied by ventilatory obstruction persisted for 4 yr	Wunderlich et al. 1982
OCCUPATIONAL EXPOSURE					
Copper smelter workers (exposed group) and mine repair	Inhalation	0.3-4 (exposed group)	Up to 20 yr	Exposed and control subjects were matched by age and smoking habits; FVC, FEV_1, FEF_{50}, and closing volume measurements from both groups were	Archer et al. 1979

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
shop workers (control group); all workers were white males.				taken before and after the work shift. Mean FEV_1 and FVC values were significantly decreased following a work shift in smelter workers in comparison to controls; more smelter workers had decreased FEV_1 and FEF_{50} values during the day; more smelter workers complained of chest tightness	
Workers in an electric refrigeration manufacturing plant; 100 workers exposed to sulfur dioxide; 100 were not exposed	Inhalation	20-30 ppm (average for exposed group)	3.82 yr (mean)	Exposed workers showed a significantly higher incidence of nasopharyngitis, of alteration in sense of smell and sense of taste, of increased sensitivity to other irritants; they also showed a significantly higher incidence of abnormal urinary acidity, of tendency to increased fatigue, of shortness of breath on exertion, and of abnormal reflexes; no demonstrable association between frequency or severity of initial symptoms and frequency of heavy exposure	Kehoe et al. 1932
Workers at a pulp mill; 54 workers were exposed to sulfur dioxide and another 54	Inhalation	2-36 ppm	NR	A significantly higher frequency of cough, expectoration, and dyspnoea on exertion was found in the exposed group; the maximal expiratory flow rate was significantly lower in the exposed group; there was no significant difference	Skalpe 1964

workers were not exposed				between exposed and nonexposed workers in vital capacity values	
147 workers at a pulp mill who were exposed to sulfur dioxide and 124 workers at a paper mill who were not exposed; pulp mill workers were co-exposed to chlorine	Inhalation	1-33 ppm	16.3 yr (exposed group)	No significant differences in the prevalence of chronic non-specifc respiratory diseases between workers exposed to sulfur dioxide and those not exposed	Ferris et al. 1967
190 broom manufacturing workers (exposed group) and 43 unexposed workers not exposed to SO_2 (control group)	Inhalation	0-0.285 ppm SO_2 (summer); 6.5-56.8 ppm SO_2 (winter). Dust concentrations 0-21 mg/m^3 (winter) and 3-27 mg/m^3 (summer).	Compared exposure during winter months versus summer months	Exposed workers reported: coughing (94.2%), dyspnea (91.0%), burning of the nose, eyes and throat (74.7%), tearing (64.7%), and substernal pain (75.3%; sulfate concentration in the urine and methemoglobin and sulfhemoglobin concentrations in the blood of exposed workers significantly higher than in controls	Savic et al. 1987
COMMUNITY EXPOSURES					
Population of London in 1950's	Inhalation	1.3 (peak SO_2 concentrations); particulate matter concentrations were reported to	5-d pollution episode	Total deaths 4,000, 3-fold higher than normal; excess deaths attributed to impaired respiratory function, including bronchitis and from cardiac effects; most deaths occurred in the elderly and in	WHO 1979

Subject	Route	Concentration (ppm)	Duration	Effect	Reference
		be at least 4.5 mg/m³		individuals with preexisting cardiac or respiratory disease	
Residents living near a pulp mill (exposed group); residents in nonpolluted community (referent group)	Inhalation	0.76-1.1 ppb (exposed community); 0.38 ppb (referent community)	March and April 1992	Increased incidence of cough, respiratory infections, headache in residents living near pulp mill as compared with referent community	Partti-Pellinen et al. 1996
Population of Athens, Greece (1984-1988)	Inhalation	0.014-0.027	1984-1988	Total mortality associated with SO_2, smoke, and CO. SO_2 and smoke independent predictors of mortality	Touloumi et al. 1994
Population of East Berlin	Inhalation	Mean = 0.063	Winters of 1981-1989	After controlling for temperature and humidity, both SO_2 and suspended particles were found to be contributors to excess mortality, the strongest association found for mortality lagged for 2 d	Rahlenbeck and Kahl 1996
2 English communities	Inhalation	0.04		Increase in lung cancer mortality in men and increases in mortality from bronchitis in men and women exposed long-term to SO_2	Wicken and Buck (1964), as cited by Clayton (1978)
	Inhalation	0.15-0.19 (with concomitant high soot concentrations)		Significant correlation observed between SO_2 concentration and deaths or disease with 24-h mean SO_2 concentrations	Joosting 1967, as cited by Clayton (1978)

1,000 men (aged 30-59)	Inhalation	0.16-0.21 (with accompanying smoke, 300-400 $\mu g/m^3$)		Significant relationship between respiratory illness and SO_2 and smoke observed.	Fletcher et al. 1968, as cited by Clayton (1978)
	Inhalation	0.11-0.19	3-4 d	Excess mortality resulted when 24-h mean SO_2 exceeded 0.19 ppm for a few days; hospital admissions and absenteeism increased when at 0.11-0.15 ppm for 3-4 consecutive days.	Brasser et al. 1967 as cited by Clayton (1978)

Abbreviations: FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, maximal expiratory flow; NR, not reported; BAL, bronchiolar alveolar lavage; RH, relative humidity; SRaw, specific airway resistance; VC, vital capacity; $V_{MAX50\%}$, 50% of vital capacity.

TABLE 9–3 Exposure of Healthy Subjects to Sulfur Dioxide

Concentration	Duration	Effect	Reference
3 ppm	7,200 min	Slight increase in small airway resistance	WHO 1979
5 ppm	10–360 min	Immediate exposures resulted in coughing and bronchoconstriction; moderate airflow resistance; threshold for minor ocular irritation	Sandstrom et al. 1989c; Andersen et al. 1974
10–16 ppm	10–30 min	Immediate exposure resulted in coughing; after acclimation, signs of irritation of pharynx, salivation, and airflow resistance	Frank et al. 1962, 1964
15 ppm	10 min	Pulmonary flow resistance of 3%	Frank 1964
25 ppm	360 min	Nearly intolerable upon initial exposure; following gradual acclimation, dryness and slight pain in nose, rhinorrhea, conjectival pain, decreased mucous flow and airflow resistance (reversible), irritation considered “never excessive”	Andersen et al. 1974
29 ppm	10 min	Pulmonary flow resistance of 18%	Frank 1964

Abbreviations: WHO, World Health Organization.

Occupational and Community Exposure Studies

Table 9–2 also presents data from occupational and epidemiologic studies that indicate that the respiratory system is the primary target for sulfur dioxide. There was variability in the study findings that probably resulted from a lack of adequate analytical measurements (use of area sampling rather than personnel monitoring); the multiplicity of confounding, concurrent exposures to other chemicals and participates; and the study indices investigated. However, some reasonable correlations between effects reported and exposure bounds can be determined.

Kehoe et al. (1932) reported no significant evidence of respiratory damage to workers reportedly exposed to sulfur dioxide concentrations of 20–30 ppm for a mean of 4 yr. The authors stated that even higher workplace airborne concentrations (80–100 ppm) occurred at the plant before the study began. There was no demonstrable association between frequency or severity of initial symptoms

(irritation, coughing, epistaxis, constriction of the chest, hemoptysis) and frequency of heavy exposure. A definite ability to acclimate to higher airborne concentrations was noted, although individual variability was found to be relatively high.

Skalpe (1964) investigated the effects of chronic sulfur dioxide exposure in Norwegian pulp mills. Individual Dräeger tubes recorded daily airborne concentrations of 2–36 ppm sulfur dioxide, although the author suggested that earlier exposures of the same individuals likely were "much higher." A higher frequency of signs of irritation (cough, expectoration, dyspnea) was observed during exertion in sulfur-dioxide-exposed versus unexposed control populations. No significant differences in vital capacity were reported.

Ferris et al. (1967) reported no significant differences in the prevalence of chronic nonspecific respiratory disease between workers in the pulp industry and workers from a paper mill, all of whom were exposed to a broad range (1–33 ppm) of sulfur dioxide and had coexposure to chlorine. It is noteworthy that when both worker populations were compared with the local population, each exhibited a lower prevalence of chronic respiratory disease than did the general public.

Community exposure studies typically included concomitant exposures to particles, so the studies have limited utility in defining causation: sulfur dioxide was but one of several agents contributing to observed effects. The epidemiologic studies suggest that the respiratory effects of exposure to sulfur dioxide in combination with particles, are greater than are the effects caused by sulfur dioxide alone in healthy individuals–especially in the elderly and those with preexisting cardiac or respiratory disease (WHO 1979).

EXPERIMENTAL ANIMAL TOXICITY DATA

Acute Exposure

Acute inhalation exposure to sulfur dioxide produces lethal and nonlethal effects in laboratory animals. Data suggest that the sensitivity of animals to sulfur dioxide varies: Rats are most resistant and guinea pigs are most sensitive. Table 9–4 lists the concentrations that produce 50% mortality in exposed animals (LC_{50}). Acute lethality at exposures greater than 100 ppm appears to be a function of concentration and duration of exposure. For example, LC_{50}s were calculated in mice exposed to nominal concentrations of 150, 1,000, and 3,000 ppm sulfur dioxide for exposure durations of 847 h, 4 h, and 30 min, respectively (Hilado and Machado 1977; U.S. Department of Health Education and Welfare 1969, as cited in ACGIH 1994).

TABLE 9–4 LC50 for Exposure to Sulfur Dioxide

Species	Duration	LC_{50} (ppm)	Reference
Mouse	30min	3,000	Hilado and Machado 1977
Mouse	4 h	1,000	U.S. Department of Health, Education and Welfare 1969 (as cited in ACGIH 1994)
Mouse	847 h	150	U.S. Department of Health, Education and Welfare 1969 (as cited in ACGIH 1994)
Rat	4 h	1,057	Cohen et al. 1973
Guinea pig	20 h	1,000	U.S. Department of Health, Education and Welfare 1969 (as cited in ACGIH 1994)
Guinea pig	154 h	130	U.S. Department of Health, Education and Welfare 1969 (as cited in ACGIH 1994)

Abbreviation: LC_{50}, median lethal concentration.

Table 9–5 presents data from various animal studies on the acute toxicity of sulfur dioxide. These studies support findings from the human studies, indicating that sulfur dioxide exerts its effect primarily on the respiratory system. Acute effects at relatively low concentrations (<20ppm) induced transient bronchoconstriction and increases in airway resistance. Higher concentrations produced more sustained biochemical, clinical, and histologic changes in the respiratory system. No material effects were noted in organs outside of the respiratory tract after acute exposure to sulfur dioxide.

No studies were found that examined effects in animals after dermal exposures to sulfur dioxide. However, data indicate that sulfur dioxide is a severe eye irritant, as sulfuric acid is formed when sulfur dioxide reacts with moist surfaces (ATSDR 1998).

Repeated Exposure

Repeated or continuous exposures to sulfur dioxide have been studied for several animal species. Data from some of these studies are summarized in Table

TABLE 9-5 Experimental Animal Toxicity Data, Exposure to Sulfur Dioxide

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Rat (CD outbred): 8, male	Inhalation	224, 593, 965, 1168, 1319	4 h	Mortality was 0/8, 0/8, 3/8, 5/8, and 8/8 for 224, 593, 965, 1,168, and 1,319 ppm, respectively.	NOAEL: 593; LOAEL: 965 (resulting in death in 3 of 8 rats within 2 wk of exposure)	Cohen et al. 1973
Rat (Wistar), male	Inhalation	800	8 h	Loss of cilia and cell necrosis in trachea and main bronchus.	LOAEL: 800	Stratmann et al. 1991
Rat (Swiss Albino): 50, male	Inhalation	0, 0.87	24 h	Hematocrit and sulfhemoglobin statistically significantly increased in comparison to controls (hematocrit: 43.55 ± 0.41% vs. 41.97 ± 0.35%; sulfhemoglobin: 0.6 ± 0.08% vs. 0.08 ± 0.02%).	LOAEL: 0.87	Baskurt 1988
Rat, males	Inhalation	0, 30	5 d/wk, 12 wk	Inflammation of bronchial mucosa.	LOAEL: 30	Krasnowska et al. 1998
Rat	Inhalation	400	3 h/d; 5 d/wk, 2-42 d	Epithelial necrosis, loss of cilia, increased numbers and activity of goblet cells.	LOAEL: 400	Lamb and Reid 1968

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Rat: 6	Inhalation	10	1 h/d, 30 d	Eye irritation.	LOAEL: 10	Haider et al. 1982
Mouse (Swiss-albino): 4	Inhalation	1,100-14,286	1-8 min	Animals monitored for time to first sign of incapacitation, time to convulsion, and time to death. Time to first sign of incapacitation was under 3 min for 3,500 to 14,300 ppm and increased to 6 min as concentration decreased to 1,100 ppm. Average time to staggering increased from 1 to 6 min. Average time to convulsion increased from 2 to 8 min as concentration decreased from 14,300 to 3,500 ppm. Average time to death increased from 3 to 8 min as concentration decreased from 14,300 to 4,800 ppm. No deaths of animals exposed to 1,190 ppm for 30 min.	LOAEL: 1,100	Hilado and Machado 1977

Mouse (ICR)	Inhalation	20	30, 60, 90, 120 min	Degenerative changes to the olfactory epithelium at 60 min.	LOAEL: 20	Min et al. 1994
Guinea pig: 10-30	Inhalation	2.6, 20, 100, 200, 750	1 h	Increased airway resistance seen at all concentrations. Increase in SRaw was 20%, 25%, 70%, 140%, and 300% at concentrations of 2.6, 20, 100, 200, and 750 ppm, respectively.	LOAEL: 2.6	Amdur 1959
Guinea pig: males	Inhalation	1	1 h	Exposed animals challenged with acetylcholine showed a significant increase in pulmonary resistance.	NOAEL: 1	Chen et al. 1992
Guinea pigs: 6	Inhalation	24	3 h	Increased airway resistance increased from 20% at the end of the first h to 86% at the end of the third hr. 3 h after exposure, resistance had returned to control levels.	LOAEL: 24	Amdur 1959
Guinea pig: females	Inhalation	5	8 h/d, 5d	Severe destruction of ciliated epithelium and polymorphonuclear infiltrates.	LOAEL: 5	Riedel et al. 1992
Guinea pig: 12	Inhalation	10	1 h/d, 30 d	Eye irritation.	LOAEL: 10	Haider 1985

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
Guinea pig	Inhalation	0.13, 1.01, 5.72	12 mo	Pulmonary function measurements indicated no adverse effects on lung mechanics.	NOAEL: 5.72	Alarie et al. 1970
Hamster	Inhalation	650	4 h/d; 5 d/wk; 19-74 d	Dilated bronchi and alveolar ducts; small scattered areas of focal emphysema.	LOAEL: 650	Goldring et al. 1970
Rabbit: 21	Inhalation	0, 0.57	10 min	Respiratory flow slightly decreased and respiratory resistance slightly increased in exposed animals.	LOAEL: 0.57	Islam and Oberbarnscheidt 1994
Rabbit: females	Inhalation	200-300	10-20 min	Transient decrease in cough reflex and Hering-Breuer inflation reflex.	LOAEL: 200-300	Hanacek et al. 1991
Rabbit: males	Inhalation	70-300	2 h/d; 6 d/wk; 5 wk	Decreased respiratory rate; rhinitis; tracheitis; bronchopneumonia; body weight gain 25% less than controls.	LOAEL 70-300	Miyata et al. 1990
Dog: 12	Inhalation	1.1-141	20-40 min	5% decreased compliance; increased resistance observed.	LOAEL: 1.1	Balchum et al. 1960b, as cited by ATSDR 1998

Dog: 10	Inhalation	1.8-148	30-40 min	8.5% decreased compliance; 150-300% increased resistance.	LOAEL: 1.8	Balchum et al. 1960b as cited in ATSDR 1998
Dog: 3 or 7	Inhalation	0, 500	1 h	Microscopic examination revealed tracheal epithelial damage in all exposed animals, but not in controls. At 1 h after exposure, injury was difficult to assess because the tracheal surfaces were covered with exfoliated cells or were in total disarray. At 6 h, lesions were well defined and large flattened cells covered the basement membranes where mucosal cells had exfoliated.	LOAEL: 500	Hulbert et al. 1989
Dog: 8 male or female	Inhalation	200	2 h	Exposure caused immediate increase in lung reactivity to histamine aerosol. Lungs most reactive immediately after exposure and lung reactivity had returned to control levels 2 h after exposure. Cells obtained from BAL increased after exposure; initially the increase was due to an increase in epithelial cells	LOAEL: 200	Jackson and Eady 1988

Species: No. per Group	Route	Concentration (ppm)	Duration	Effect	NOAEL, LOAEL (ppm)	Reference
				(0.25 and 1 h) and later by neutrophils (1, 2, 3, and 4 h). No changes observed in lymphocyte, macrophage, eosinophils, goblet cells or mast cells in fluid lavage.		
Dog: 12	Inhalation	500	2 h/d, 5 d/wk, 21 wk	Exposure caused chronic bronchitis and conjunctivitis. Complete recovery occurred within 5 wk after exposure cessation.	LOAEL: 500	Greene et al. 1984
Monkey	Inhalation	0.14, 0.64, 1.28	24 h/d, 7 d/wk, 78 wk	No alteration in pulmonary function.	NOAEL: 1.28	Alarie et al. 1972
Monkey	Inhalation	5.1	23.3 h/d, 7 d/wk, 78 wk	No alteration in pulmonary function.	NOAEL: 5.1	Alarie et al. 1975

Abbreviations: BAL bronchiolar alveolar lavage; LOAEL, lowest observable adverse effect level; NOAEL, no observed adverse effect level; SRaw, specific airway resistance.

9–5. Rats exposed to sulfur dioxide up to 400 ppm for less than 90 d showed a thickening of the mucous layer in the trachea and an increase in goblet cells and mucous glands that is similar to human chronic bronchitis (Krasnowska et al. 1998; Lamb and Reid 1968). Animal studies at exposure concentrations below 10 ppm demonstrated reversible functional abnormalities. Chronic exposures (>90 d) at 500 ppm resulted in bronchitis and conjunctivitis in dogs (Greene et al. 1984), but exposure at 650 ppm for up to 74 d produced intense sensory irritation and histologic changes in the lungs and bronchi of hamsters (Goldring et al. 1970). Guinea pigs exposed at nearly 6 ppm for 12 mo and monkeys at 1.3 ppm for 20 mo exhibited no adverse respiratory effects (Alarie et al. 1970). At 5 ppm, dogs showed an increase in pulmonary upper airway resistance and decreased lung compliance (Balchum et al. 1959). Irritation effects seen in these animal studies diminished with repeat exposures, suggesting an adaptive response, an occurrence also shown in humans (Dept. of Labor 1975, as cited in ATSDR 1998). Substantive repeated dosing effects of sulfur dioxide exposure was limited to effects on the respiratory system.

MECHANISM OF ACTION

Sulfur dioxide induces airway resistance as a result of reflex bronchoconstriction (Frank et al. 1962; Nadel et al. 1965) and respiratory inhibition that is mediated through vagal reflexes by cholinergic and noncholinergic mechanisms. Noncholinergic components include but are not limited to tachykinins, leukotrienes, and prostaglandins. The extent to which cholinergic or noncholinergic mechanisms contribute to sulfur dioxide-induced effects is not known and could vary between people with and without asthma and among animal species.

Early study of bronchoconstricitive mechanisms of sulfur dioxide with ventilated, tracheostomized cats indicated that pulmonary resistance increased during the first breath but reversed rapidly (Nadel et al. 1965). Intravenous injection of atropine (a parasympathetic receptor blocker) or cooling of the cervical vagosympathetic nerves abolishes bronchoconstriction; rewarming the nerve reestablishes the response. The rapidity of the response and its reversal emphasize the parasympathetically mediated tonal change in smooth muscle. Studies with human subjects have confirmed the predominance of parasympathetic mediation, but histamine from inflammatory cells could play a secondary role in the bronchoconstrictive responses of people with asthma (Sheppard et al. 1981).

Sheppard (1988) examined the chemical mechanisms that underlie the bronchoconstrictive effect of sulfur dioxide. Sulfur dioxide dissolves in water to form bisulfite ion, sulfite ion, and hydrogen ion. The bisulfite ion is a nucleophile that can disrupt disulfite bonds. It has been postulated that bisulfite

formed at the airway surface during inhalation of sulfur dioxide initiates bronchoconstriction by disrupting disulfide bonds in tissue proteins.

NAVY'S RECOMMENDED SEALS

The Navy proposes a SEAL 1 of 3 ppm. The SEAL 1 of 3 ppm appears to be based on the study by Weir et al. (1972). In this study 12 healthy, adult males exposed continuously to less than 1 ppm for 120 h experienced no adverse effects; however, at 3 ppm, the subjects experienced slightly increased airway resistance. That information was only included in an abstract and no data was presented. Thus, no definitive dose-response information could be derived.

The Navy's proposed SEAL 2 for exposure to sulfur dioxide is 6 ppm. The Navy did not describe how it derived this SEAL, although it could have been derived from a study by Andersen et al. (1974), who exposed 15 males at 1, 5, and 25 ppm for 6 h, and observed a significant decrease in nasal mucous flow rate and an increase in nasal airflow resistance in subjects exposed at 5 and 25 ppm for 6 h. A decrease in forced expiratory volume at 1 s and in forced expiratory flow during the middle half of expired flow volume was observed in the subjects exposed at all concentrations.

ADDITIONAL RECOMMENDATIONS FROM THE NRC AND OTHER ORGANIZATIONS

The recommended exposure limits of other organizations are presented in Table 9–6. The 24-h emergency exposure guidance level (EEGL) is the most relevant guidance level to compare to the SEALs (NRC 1984). EEGLs were developed for healthy military personnel for emergency situations. An important difference between EEGLs and SEALs is that EEGLs allow mild, reversible health effects, whereas SEALs allow moderate, reversible health effects. That is, SEALs allow effects that are somewhat more intense or potent than those for EEGLs. Therefore, the SEALs are higher than the corresponding EEGLs.

SUBCOMMITTEE ANALYSIS AND RECOMMENDATIONS

The toxic effect of particular concern associated with sulfur dioxide exposure is irritation of the upper respiratory tract, and it is considered to be of a localized nature. There is no evidence of systemic toxicity or organ system effects; hence, irritation appears the sole effect of concern.

TABLE 9–6 Recommendations from Other Organizations for Sulfur Dioxide

Organization	Type of Exposure Level	Recommended Exposure Level (ppm)	Reference
ACGIH	TLV	2	ACGIH (1994)
	STEL	5	
AIHA	ERPG-1	0.3	AIHA 2001
	ERPG-2	3	
	ERPG-3	15	
ATSDR	Acute MRL	0.01	ATSDR (1998)
DFG	MAK (8 h/d during 40-h workweek)	2	DFG 1997
	Peak limit (5 min maximum duration, 8 times per shift)	4	
EPA	NAAQS (24 h)	0.14 (365 mg/m^3)	EPA (1998)[a]
	NAAQS (annual arithmetic mean)	0.03 (80 mg/m^3)	
NIOSH	REL	2	NIOSH (2000)
	STEL	5	
	IDLH	100	
NRC	EEGL (10 min)	30	NRC (1984)
	EEGL (30 min)	20	
	EEGL (1 h)	10	
	EEGL (24 h)	5	
	CEGL (90 d)	1	
OSHA	PEL-TWA (8 h)	2	OSHA (1998)

[a]National Primary Ambient Air Quality Standards for Sulfur Oxides (Sulfur Dioxide). 40 CFR 50.4.
Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AIHA, American Industrial Hygiene Association; ATSDR, Agency for Toxic Substances and Disease Registry; CEGL, community exposure guidance level; DFG, Deutsche Forschungsgemeinshaft; EEGL, emergency exposure guidance level; EPA, Environmental Protection Agency, IDLH, immediately dangerous to life and health; MAK, maximum concentration values in the workplace; MRL, minimal risk level; NAAQS, National Ambient Air Quality Standard; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL-TWA, permissible exposure limit-time-weighted average; REL, recommended exposure limit; STEL, short-term exposure limit; TLV, Threshold Limit Value.

Many of the biologic responses seen at lower concentrations are judged to pose a lesser degree of concern than would be associated with the risks attendant to emergency evacuation from a disabled submarine. Hence, a considerable tolerance to development of such responses is considered acceptable. The effects generally noted—including lung airflow, bronchoconstriction, and mucous secretion—are reversible after exposure cessation and are not considered to significantly affect long-term health of survivors. They also are considered insufficient to adversely affect escape.

It is recognized that respiratory irritation caused by sulfur dioxide exposure becomes objectionable immediately when the gas is encountered at relatively low concentrations; relatively rapid acclimation, however, occurs with continued exposure, and gradual increases result in tolerance of concentrations that would be intolerable if encountered directly (Andersen et al. 1974).

Considerable weight has been given to occupational exposure information, which used longer term, substantively higher sulfur dioxide exposures than were used in many of the controlled human exposure studies. The occupational data are considered particularly valuable in providing practical information about the relationships of concentration and time course, tolerance, and acclimation to irritant effects caused by sulfur dioxide exposures in a healthy human population—as would be more closely representative of the population found in a submarine.

Submarine Escape Action Level 1

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 1 of 3 ppm for sulfur dioxide is too conservative. The subcommittee recommends a SEAL 1 of 20 ppm. The subcommittee's recommendation is supported by several occupational studies that show tolerance to irritant effects from repeated exposures at 20 ppm (Ferris et al. 1967; Kehoe et al. 1932; Skalpe 1964). It is also supported by a study in which volunteers showed tolerance to a 6-h exposure at 25 ppm (Andersen et al. 1974) and minimal pulmonary flow resistance to a 10-min nose-only exposure at 15 or 29 ppm (Frank 1964). Effects on mucus flow and airflow resistance are to be expected at exposure concentrations of 20 ppm (Frank et al. 1964), however, they should not impair the submariners' ability to escape. Healthy submariners should be able to tolerate irritative effects associated with exposures to less than 20 ppm for up to 10 d.

Submarine Escape Action Level 2

On the basis of its review of human and experimental animal health-effects and related data, the subcommittee concludes that the Navy's proposed SEAL 2 of 6 ppm for sulfur dioxide is too conservative. The subcommittee recommends a SEAL 2 of 30 ppm. The subcommittee's recommended SEAL 2 is based on an occupational study in which workers exposed to 30 ppm for several years tolerated the irritative effects of sulfur dioxide (Kehoe et al. 1932). The crew of a disabled submarine should be able to tolerate the irritative effects from exposure to sulfur dioxide at concentrations below 30 ppm for up to 24 h.

DATA GAPS AND RESEARCH NEEDS

Little information is available to substantiate respiratory irritation effects above 30 ppm or that thoroughly investigate the interaction of sulfur dioxide and airborne particulates. Some evidence suggests that interactive effects are possible, but there is insufficient information to differentiate between sensory, functional, or physiologic effects and exposure concentration. Because the effects of concern are primarily upper respiratory rather than systemic or involving the deep lung, additional research on systemic and lower respiratory-tract effects is not expected to add materially to these recommendations. Data from animal studies suggest that a lack of prior exposure to sulfur dioxide may intensify its irritative effects from a modest exposure and therefore, the Navy should conduct research examining the adaptive effects of sulfur dioxide exposure.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1994. Threshold Limit Value for Chemical Substances and Physical Agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 2001. The AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook Fairfax, VA: American Industrial Hygiene Association.

Alarie, Y., C.E.Ulrich, W.M.Busey, H.E.Swann Jr, and H.N.MacFarland. 1970. Long-term continuous exposure of guinea pigs to sulfur dioxide. Arch. Environ. Health 21(6):769–777.

Alarie, Y., C.E.Ulrick, W.M.Busey, A.A.Krumm, and H.N.MacFarland. 1972. Long-term continuous exposure to sulfur dioxide in cynomolgus monkeys. Arch. Environ. Health 24 (2):115–127.

Alarie, Y.C., A.A.Krumm, W.M.Busey, C.E.Urich, and R.J.Kantz. 1975. Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures. Results of studies in monkeys and guinea pigs. Arch. Environ. Health 30(5):254–262.

Amdur, M.O. 1959. The physiological response of guinea pigs to atmospheric pollutants. Int. J. Air Pollut. 1:170.

Amdur, M.O. 1969. Toxicologic appraisal of particulate matter, oxides of sulfur, and sulfuric acid. J. Air Pollut. Control Assoc. 19(9):638–644.

Amdur, M.O., W.W.Melvin, and P.Drinker. 1953. Effects of inhalation of sulfur dioxide by man. Lancet 2(Oct.10):758–759.

Andersen, I.B., G.R.Lundqvist, P.L.Jensen, and D.F.Proctor. 1974. Human response to controlled levels of sulfur dioxide. Arch. Environ. Health 28(1):31–39.

Archer, V.E., C.D.Fullmer, and C.H.Castle. 1979. Sulfur dioxide exposure in a smelter: III. Acute effects and sputum cytology. J. Occup. Med. 21(5):359–364.

ATSDR (Agency for Toxic Substances Disease Registry). 1998. Toxicological Profile for Sulfur Dioxide. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances Disease Registry, Atlanta, GA.

Balchum, O.J., J.Dybicki, and R.Meneely. 1959. Absorption and distribution of 35 sulfur dioxide inhaled through the nose and mouth by dogs. Am. J. Physiol. 197:1317–1321.

Balchum, O.J., J.Dybicki, and G.R.Meneely. 1960a. The dynamics of sulfur dioxide inhalation, absorption, distribution and retention. Arch. Ind. Health 21:564–569.

Balchum, O.J., J.Dybicki, and G.R.Meneely. 1960b. Pulmonary resistance and compliance with concurrent radioactive sulfur distribution in dogs breathing sulfur dioxide. J. Appl. Physiol. 15:62–66.

Balmes, J.R., J.M.Fine, and D.Sheppard. 1987. Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am. Rev. Respir. Dis. 136(5):1117–1121.

Baskurt, O.K. 1988. Acute hematologic and hemorheologic effects of sulfur dioxide inhalation. Arch. Environ. Health 43(5):344–348.

Brasser, L.J., P.E.Joosting, and D.van Zuilen. 1967. Sulfur dioxide—to what level is it acceptable? Report No. G-300. Research Institute for Public Health Engineering, Delft, Netherlands. July.

Budavari S., ed. 1989. Sulfur dioxide. Pp. 8,950 in The Merck Index, 11th Ed. Rahway, NJ: Merck.

Cabre, F., C.Marin, M.Cascante, and E.I.Canela. 1990. Occurrence and comparison of sulfite oxidase activity in mammalian tissues. Biochem. Med. Metab. Biol. 43(2):159–162.

Charan, N.B., C.G.Myers, S.Lakshminarayan, and T.M.Spencer. 1979. Pulmonary injuries associated with acute sulfur dioxide inhalation. Am. Rev. Respir. Dis. 119(4):555–560.

Chen, L.C., P.D.Miller, M.O.Amdur, and T.Gordon. 1992. Airway hyper responsiveness in guinea pigs exposed to acid-coated ultrafine particles. J. Toxicol. Environ. Health 35(3):165–174.

Clayton, G.D. 1978. Air pollution. Pp. 595–652 in Patty's Industrial Hygiene and Toxicology, Vol. 1. General Principle, 3rd Rev. Ed., G.D.Clayton and F.E.Clayton, eds. New York: John Wiley & Sons.

Cohen, H.J., R.T.Drew, J.L.Johnson, and K.V.Rajagopalan. 1973. Molecular basis of the biological function of molybdenum: The relationship between sulfite oxidase and the acute toxicity of bisulfite and SO_2. Proc. Natl. Acad. Sci. 70(12):3655–3659.

Costa, D.L., and M.O.Amdur. 1996. Air pollution. Pp. 857–882 in Cassarett and Doull's Toxicology, the Basic Science of Poisons, 5th Ed., C.D.Klaassen, ed. New York: McGraw-Hill.

Constantin, D., A.Bini, E.Meletti, P.Moldeus, D.Monti, and A.Tomasi. 1996. Age-related differences in the metabolism of sulphite to sulphate and in the identification of sulphur trioxide radical in human polymorphonuclear leukocytes. Mech. Ageing. Dev. 88(1–2):95–109.

Dalhamn, T., and T.Strandberg. 1961. Acute effect of sulfur dioxide on the rate of ciliary beat in the trachea of rabbit, in vivo and in vitro, with studies in the absorptional capacity of the nasal cavity. Int. J. Air Water Pollut. 4(3/4):154–167.

Department of Labor. 1975. Occupational exposure to sulfur dioxide. Fed. Regist. 40:54520–54534.

Dautrebande, L., and R.Capps. 1950. Studies on aerosols. IX. Enhancement of irritating effects of various substances on the eye, nose, and throat by particulate matter and liquid aerosols. Arch. Int. Pharmacodyn. 82:505–528.

DFG (Deutsche Forschungsgemeinschaft). 1997. List of MAK and BAT Values 1997. Maximum Concentrations and Biological Tolerance Values at the Workplace, 1st Ed. Report No. 33. Weinheim: Wiley-VCH.

Douglas, R.B., and J.E.Coe. 1987. The relative sensitivity of the human eye and lung to irritant gases. Ann. Occup. Hyg. 31(2):265–267.

EPA (U.S. Environmental Protection Agency). 1982. Air Quality Criteria for Particulate Matter and Sulfur Oxides, Vol. III. EPA-600/8–82–029c. Environmental Criteria and Assessment Office, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC. December.

EPA (U.S. Environmental Protection Agency). 1994a. Review of the National Ambient Air Quality Standards for Sulfur Oxides: Assessment of Scientific and Technical Information. Supplement to the 1986 OAQPS Staff Paper Addendum. EPA-452/R-94–013. Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. PB95–124160.

EPA (U.S. Environmental Protection Agency). 1994b. Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982). Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals. EPA/600/FP-93/002. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC. August.

Ferris, B.G., W.A.Burgess, and J.Worcester. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States . Br. J. Ind. Med. 24(1):26– 37.

Fletcher, C.M., C.M.Tinker, I.D.Hill, and F.E.Speizer. 1968. A Five-Year Perspective Field Study of Early Obstructive Airway Disease. Current Research in Chronic Respiratory Disease. Proceedings of the 11th Aspen Conference, Department of

Health, Education and Welfare, Public Health Service, Washington, DC.

Frank, N.R. 1964. Studies on the effects of acute exposure to sulphur dioxide in human subjects. Proc. Royal Soc. Med. 57:1029–1033.

Frank, N.R., M.O.Amdur, J.Worcester, and J.L.Whittenberger. 1962. Effects of acute controlled exposure to sulfur dioxide on respiratory mechanics in healthy male adults. J. Appl. Physiol. 17(2):252–258.

Frank, N.R., M.O.Amdur, and J.L.Whittenberger. 1964. A comparison of the acute effects of SO2 administered alone or in combination with NaCl particles in the respiratory mechanics of healthy adults. Int. J. Air Water Poll. 8:125–133.

Frank, N.R., R.E.Yoder, E.Yokoyama, and F.E.Speizer. 1967. The diffusion of $^{35}SO_2$ from tissue fluids into the lungs following exposure of dogs to ^{35}sulfur dioxide. Health Physics 13:31–38.

Frank, N.R., R.E.Yoder, J.D.Brain, and E.Yokoyama. 1969. Sulfur dioxide (^{35}S-labeled) absorption by the nose and mouth under conditions of varying concentration and flow. Arch. Environ. Health 18(3):315–322.

Galea, M. 1964. Fatal sulfur dioxide inhalation. Can. Med. Assoc. J. 91:345–347.

Goldring, I.P., L.Greenburg, S.S.Park, and I.M.Ratner. 1970. Pulmonary effects of sulfur dioxide exposure in the Syrian hamster. II. Combined with emphysema. Arch. Environ. Health 21 (1):32–37.

Gong, H., P.A.Lachenbruch, P.Harber, and W.S.Linn. 1995. Comparative short-term health responses to sulfur dioxide exposure and other common stresses in a panel of asthmatics. Toxicol. Ind. Health 11(5):467–487.

Greene, S.A., R.K.Wolff, F.F.Hahn, R.F.Henderson, J.L.Mauderly, and D.L. Lundgren. 1984. Sulfur dioxide-induced chronic bronchitis in beagle dogs. J. Toxicol. Environ. Health 13(4–6):945–958.

Gunnison, A.F., and E.D.Palmes. 1974. S-sulfonates in human plasma following inhalation of sulfur dioxide. Am. Ind. Hyg. Assoc. J. 35(5):288–291.

Gunnison, A.F., A.Sellakumar, D.Currie, and E.A.Snyder. 1987. Distribution, metabolism and toxicity of inhaled sulfur dioxide and endogenously generated sulfite in the respiratory tract of normal and sulfite oxidase-deficient rats. J. Toxicol. Environ. Health 21(1–2):141–162.

Haider, S.S. 1985. Effects of exhaust pollutant sulfur dioxide on lipid metabolism of guinea pig organs. Ind. Health 23(2):81–87.

Haider, S.S., M.Hasan, and N.H.Khan. 1982. Air pollutant sulfur dioxide-induced alterations on the levels of lipids, lipid peroxidation and lipase activity in various regions of the rat brain. Acta Pharmacol Toxicol. 51(1):45–50.

Hanacek, J., K.Adamicova, J.Briestenska, and D.Jankovska. 1991. Cough reflex in rabbits 24-h and 48-h after sulphur dioxide breathing. Acta Physiol. Hung. 77(2):179–185.

Harkonen, H., H.Nordman, O.Korhonen, and I.Winblad. 1983. Long-term effects of exposure to sulfur dioxide. Lung function four years after a pyrite dust explosion. Am. Rev. Respir. Dis. 128(5):890–893.

Hilado, C.J., and A.M.Machado. 1977. Effect of sulfur dioxide on Swiss albino mice. J. Combust. Toxicol. 4:236–245.

Horstman, D., L.J.Roger, H.Kehrl, and M.Hazucha. 1986. Airway sensitivity of asthmatics to sulfur dioxide. Toxicol. Ind. Health 2(3):289–298.

HSDB (Hazardous Substances Data Bank). 2000. Sulfur Dioxide. [Online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~BAAPUaqKu:1 [May 22, 2000].

Hulbert, W.C., S.F.Man, M.K.Rosychuk, G.Braybrook, and J.G.Mehta. 1989. The response phase—the first six hours after acute airway injury by SO_2 inhalation: An in vivo and in vitro study. Scanning Microsc. 3(1):369–378.

Islam, M.S., and J.Oberbamscheidt. 1994. The effect of a short-term SO_2 exposure on the respiratory function of sensitized non-anesthetized rabbits, [in German]. Zentralbl. Hyg. Umweltmed. 196(2):104–113.

Jackson, D.M., and R.P.Eady. 1988. Acute transient SO2-induced airway hyper reactivity: Effects of nedocromil sodium. J. Appl. Physiol. 65(3):1119–1124.

Joosting, P.E. 1967. Ingenieur. 70:50, A739. (as cited by Clayton 1978).

Jörres, R., and H.Magnussen. 1990. Airways reponse of asthmatics after a 30 min exposure, at resting ventilation, to 0.25 ppm NO_2 or 0.5 ppm SO_2. Eur. Respir. J. 3(2):132–137.

Kågedal, B., M.Källberg, and B.Sörbo. 1986. A possible involvement of glutathione in the detoxification of sulfite. Biochem. Biophys. Res. Commun. 136(3):1036–1041.

Kehoe, R.A., W.F.Machle, K.Kitzmiller, and T.J.LeBlanc. 1932. On effects of prolonged exposure to sulphur dioxide. J. Ind. Hyg. 14(5):159–173.

Koenig, J.Q., W.E.Pierson, and R.Frank 1980. Acute effects of inhaled sulfur dioxide plus sodium chloride droplet aerosol on pulmonary function in asthmatic adolescents. Environ. Res. 22 (1):145–153.

Krasnowska, M., A.Kwasniewski, J.Rabczynski, A.Fal, and J.Kuryszko. 1998. Effect of heparin on the course of sulphur dioxide induced bronchitis in rats. Arch. Immunol. Then. Exp. (Warsz) 46(1):17–24.

Kulle, T.J., L.R.Sauder, F.Shanty, H.D.Kerr, B.P.Farrell, W.R.Miller, and J.H.Milman. 1984. Sulfur dioxide and ammonium sulfate effects on pulmonary function and bronchial reactivity in human subjects. Am. Ind. Hyg. Assoc. J. 45(3):156–161.

Lamb, D., and L.Reid. 1968. Mitotic rates, goblet cell increase and histochemical changes in mucus in rat bronchial epithelium during exposure to sulphur dioxide. J. Pathol. Bacteriol. 96 (1):97–111.

Langley-Evans, S.C., G.J.Phillips, and A.A.Jackson. 1996. Sulfur dioxide: A potent glutathione depleting agent. Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol. 114(2):89–98.

Lawther, P.J., A.J.Macfarlane, R.E.Waller, and A.G.Brooks. 1975. Pulmonary function and sulfur dioxide, some preliminary findings. Environ. Res. 10(3):355–367.

Linn, W.S., D.A.Shamoo, K.R.Anderson, J.D.Whynot, E.L.Avol, and J.D.Hackney. 1985. Effects of heat and humidity on the responses of exercising asthmatics to sulfur dioxide exposure. Am. Rev. Respir. Dis. 131(2):221–225.

Min, Y.G., C.S.Rhee, M.J.Choo, H.K.Song, and S.C.Hong. 1994. Hystopathologic changes in the olfactory epithelium in mice after exposure to sulfur dioxide. Acta Otolaryngol. 114 (4):447–452.

Miyata, T., T.Ishii, N.Sugiyama, Y.Okano, N.Nishi, K.Takahama, S.Ogasawara, Y. Oda, K.Yokoyama, Y.Murata, et al. 1990. Effect of N-acetylneuraminic acid on respiratory tract secretion and inflammation in the bronchitic rabbit. Arch. Int. Pharmacodyn. Ther. 304:277–289.

Nadel, J.A., H.Salem, B.Tamplin, and Y.Tokiwa. 1965. Mechanism of bronchoconstriction during inhalation of sulfur dioxide. J. Appl. Physiol. 20(1):164–167.

NIOSH (National Institute for Occupational Safety and Health). 2000. Pocket Guide to Chemical Hazards. Cincinnati, OH: National Institute for Occupational Safety and Health. [Online]. Available: http://www.cdc.gov/niosh/npg/npg.html [April 30, 2001].

NRC (National Research Council). 1984. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

Partti-Pellinen, K., O.Martilla, V.Vilkka, J.J.Jaakkola, P.Jappinen, and T.Haahtela. 1996. The South Karelia Air Pollution Study: Effects of low-level exposure to malodorous sulfur compounds on symptoms. Arch. Environ. Health. 51(4):315– 320.

Rabinovitch, S., N.D.Greyson, W.Weiser, and V.Hoffstein. 1989. Clinical and laboratory features of acute sulfur dioxide inhalation poisoning: Two-year follow-up. Am Rev. Respir. Dis. 139 (2)556–558.

Rahlenbeck, S.I., and H.Kahl. 1996. Air population and mortality in East Berlin during the winters of 1981–1989. Int. J. Epidemiol. 25(6):1220–1226.

Riedel, F., S.Naujukat, J.Ruschoff, S.Petzoldt, and C.H.Rieger. 1992. SO_2-induced enhancement of inhalative allergic sensitization: inhibition by anti-inflammatory treatment. Int. Arch. Allergy Immunol. 98(4):386–391.

Roger, L.J., H.R.Kehrl, M.Hazucha, and D.H.Horstman. 1985. Bronchoconstriction in asthmatics exposed to sulfur dioxide during repeated exercise. J. Appl. Physiol. 59(3):784–791.

Rondinelli, R.C., J.Q.Koenig, and S.G.Marshall. 1987. The effects of sulfur dioxide on pulmonary function in healthy nonsmoking male subjects aged 55 years and older. Am. Ind. Hyg. Assoc. J. 48(4):299–303.

Sandstrom, T., B.Kolmodin-Hedman, N.Stjernberg, M.C.Andersson, and G. Lofvenius. 1988. Challenge test for sulfur dioxide-symptoms and lung function measurements. Scan. J. Work Environ. Health. 14(suppl.1):77–79.

Sandstrom, T., N.Stjernberg, M.C.Andersson, B.Kolmodin-Hedman, K.Lindstrom, and L.Rosenhall. 1989a. Is the short-term limit value for sulfur dioxide exposure safe? Effects of controlled chamber exposure investigated with bronchoalveolar lavage. Br. J. Ind. Med. 46(3):200–203.

Sandstrom, T., N.Stjernberg, M.C.Andersson, B.Kolmodin-Hedman, R.Lundgren, L. Rosenhall, and T.Angstrom. 1989b. Cell response in bronchoalveolar lavage fluid after exposure to sulfur dioxide: A time-response study. Am. Rev. Respir. Dis. 140(6):1828–1831.

Sandstrom, T., N.Stjernberg, M.C.Andersson, B.Kolmodin-Hedman, K.Lindstrom, and L.Rosenhall. 1989c. Cell response in bronchoalveolar lavage fluid after sulfur dioxide exposure. Scand. J. Work Environ. Health 15(2):142–146.

Savic, M., J.Siriski-Sasic, and D.Djulizibaric. 1987. Discomforts and laboratory findings in workers exposed to sulfur dioxide. Int. Arch. Occup. Environ. Health 59(5):513– 518.

Schachter. E.N., T.J.Witek Jr, G.J.Beck, H.B.Hosein, G.Colice, B.P.Leaderer, and W. Cain. 1984. Airway effects of low concentrations of sulfur dioxide: Dose-response characteristics. Arch. Environ. Health 39(1):34–42.

Seinfeld, J.H. 1986. Atmospheric Chemistry and Physics of Air Pollution. New York: Wiley.

Sheppard, D. 1988. Mechanisms of airway responses to inhaled sulfur dioxide. Pp. 49– 65 in Pathophysiology and Treatment of Inhalation Injuries, Lung Biology in Health and Disease, Vol. 34., J.Loke, ed. New York, NY: Marcel Dekker.

Sheppard, D., A.Saisho, J.A.Nadel, and H.A.Boushey. 1981. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. Am. Rev. Respir. Dis. 123(5):486–491.

Skalpe, I.O. 1964. Long-term effects of sulphur dioxide exposure in pulp mills. Br. Ind. Med. 21:69–73.

Speizer, F.E., and N.R.Frank 1966. The uptake and release of sulfur dioxide by the human nose. Arch Environ Health. 12(6):725–728.

Stacy, R.W., D.House, M.Friedman, M.Hazucha, J.Green, L.Raggio, and L.J.Roger. 1981. Effects of 0.75 ppm sulfur dioxide on pulmonary function parameters of normal human subjects. Arch. Environ. Health 36(4):172–178.

Strandberg, L.G. 1964. Sulfur dioxide absorption in the respiratory tract. Studies on the absorption in rabbits, its dependence on concentration and breathing phase. Arch. Environ. Health 9:160–166.

Stratmann, U., R.R.Lehmann, T.Steinbach, and G.Wessling. 1991. Effect of sulfur dioxide inhalation on the respiratory tract of the rat. Zentralbl. Hyg. Umweltmed. 192(4):324–335.

Touloumi, G., S.J.Pocock, K.Katsouyanni, and D.Trichopoulos. 1994. Short-term effects of air pollution on daily mortality in Athens: A time-series analysis. Int. J. Epidemiol. 23(5):957–967.

U.S. Department of Health, Education and Welfare. 1969. Air Quality Criteria for Sulfur Oxides. National Air Pollution Control Administration Pub. No. AP-50. DHEW, Washington, DC.

Weir, F.W., D.H.Stevens, and P.A.Bromberg. 1972. Pulmonary function studies of men exposed for 120 hours to sulfur dioxide. Toxicol. Appl. Pharmacol. 22:319.

WHO (World Health Organization). 1979. Sulfur Oxides and Suspended Particulate Matter, Environmental Health Criteria 8. Geneva: World Health Organization.

WHO (World Health Organization). 1984. Sulfur dioxide. Pp. 115–150 in Recommended Health-Based Occupational Exposure Limits for Respiratory Irritants. WHO Technical Report Series 707. Geneva: World Health Organization.

Wicken, A.J., and S.F.Buck 1964. Report on a Study of Environmental Factors Associated with Lung Cancer and Bronchitis Mortality in Areas of North East England. Research Paper No. 8. Tobacco Research Council, London.

Wunderlich, V.P., W.Leupold, W.Mittenzwey, and E.Rupprecht. 1982. Severe lung damage by inhalation of sulfur dioxide. [in German]. Dtsch. Gesundheits Wes. 37(11):519–524.

Yokoyama, E., R.E.Yoder, and N.R.Frank 1971. Distribution of 3S in the blood and its excretion in urine in dogs exposed to 35 sulfur dioxide. Arch. Environ. Health 22(3):389–395.

10

Conclusions and Recommendations

After reviewing the available data on ammonia, carbon monoxide, chlorine, hydrogen chloride, hydrogen cyanide, hydrogen sulfide, nitrogen dioxide, and sulfur dioxide, the subcommittee concludes that the Navy's proposed SEALs would be protective of the health of personnel in a disabled submarine with the exception of the SEALs for chlorine. In addition, the subcommittee concludes that the SEALs for the gases except chlorine could be set at levels higher than the Navy's proposed levels and still be protective of the health of crew members in a disabled submarine; eye or respiratory-tract irritation or central-nervous-system effects would not be intolerable or impair performance of specific tasks, including the ability to escape. A comparison of the subcommittee's recommended SEALs with the Navy's proposed SEALs is presented in Table 10–1. In addition to the research needs identified for each gas in Chapters 2–9, the subcommittee also has several additional recommendations that are presented in this chapter.

The subcommittee recommends that additional research be conducted on the health effects of mixtures of the irritant gases—ammonia, chlorine, hydrogen chloride, hydrogen sulfide, nitrogen dioxide, sulfur dioxide. The subcommittee also recommends additional studies be conducted on the combined effects of hydrogen cyanide, carbon monoxide, and hydrogen sulfide.

As described in Chapter 1, the Navy has developed instructions for the management of toxic gases in disabled submarines. Those instructions use a Cumulative Exposure Index (CEI) approach, which assumes that the effects of

exposure to the irritant gases—ammonia, chlorine, hydrogen chloride, nitrogen dioxide, and sulfur dioxide—are additive and not synergistic. The subcommittee believes that hydrogen sulfide should be considered an irritant gas and added to the CEI. The subcommittee also believes that a separate CEI should be established for carbon monoxide and hydrogen cyanide because the effects of exposure to these gases maybe additive as well. If the results of research conducted on the health effects from exposures to mixtures of gases show that the effects are not additive, then the CEI approach will have to be modified accordingly.

TABLE 10–1 Comparison of the Navy's Proposed SEALs with the Subcommittee's Recommended SEALs

	Navy's Proposed SEALs (ppm)[a]		Subcommittee's Recommended SEALs (ppm)[b]	
Gas	SEAL 1	SEAL 2	SEAL 1	SEAL 2
Ammonia	25	75	75	125
Carbon monoxide	75	85	125	150
Chlorine	2	5	1	2.5
Hydrogen chloride	2.5	25	20	35
Hydrogen cyanide	1	4.5	10	15
Hydrogen sulfide	10	20	15	30
Nitrogen dioxide	0.5	1	5	10
Sulfur dioxide	3	6	20	30

[a]U.S. Navy (1998)

[b]The Subcommittee's recommended SEALs are for an atmospheric pressure of 1 at 25°C. Values obtained for the gases using Dräeger tubes or other measurement devices in a disabled submarine might need to be corrected to an atmospheric pressure of 1 and 25°C.

The effects of environmental conditions (e.g., humidity, temperature, and pressure) found on a disabled submarine on the toxicity of the gases should be studied. Also, because fires on a disabled submarine will generate participate matter, research should be conducted on the effects of particles on the toxicity of the gases.

As noted in Chapter 1, the Navy instructs crew members wearing EABs to remove them each hour, as concentrations of some of the gases should decrease overtime because of contact with the wet surfaces likely to be found in a disabled submarine. That same logic leads the subcommittee to recommend that the concentrations of all gases be determined as frequently as possible.

The subcommittee emphasizes that its recommended SEALs are for normal atmospheric conditions (an atmospheric pressure of 1 and a temperature of 25°C). Values obtained for gas concentrations using Dräeger tubes in a disabled submarine might need to be corrected to an atmospheric pressure of 1 and 25°C. The subcommittee did not find information on the effects of hyperbaric conditions on Dräeger-tube measurements and recommends that research be conducted to determine the effect of increased pressure on Dräeger-tube measurements.

Currently, Dräeger tubes are the only means available on submarines for measuring gas concentrations once the spectrophotometers stop functioning because of power loss. Dräeger tubes have an error rate of about 30% (i.e., the indicated value maybe 30% lower or higher than the actual gas concentration), and a new tube is required for each measurement of an individual gas. The subcommittee recommends that the Navy place high priority on developing a battery-operated instrument for use in submarines to more accurately measure the gases and allow for frequent measurement of the gases in disabled submarines.

REFERENCES

U.S. Navy. 1998. Memorandum from N.A. Carlson, Acting Commanding Officer, Naval Submarine Medical Research Laboratory to Officer in Charge, Naval Medical Research Institute Toxicity Detachment. Subject: The Management of Toxic Gases in a Disabled Submarine. March 2, 1998.